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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 219/06, 401/12
A61K 31/435, 31/47

A1

(11) International Publication Number: **WO 92/12132**

(43) International Publication Date: 23 July 1992 (23.07.92)

(21) International Application Number: PCT/EP92/00020

(22) International Filing Date: 7 January 1992 (07.01.92)

(30) Priority data:

9100628.8	11 January 1991 (11.01.91)	GB
9100637.9	11 January 1991 (11.01.91)	GB
9115956.6	24 July 1991 (24.07.91)	GB
9115981.4	24 July 1991 (24.07.91)	GB

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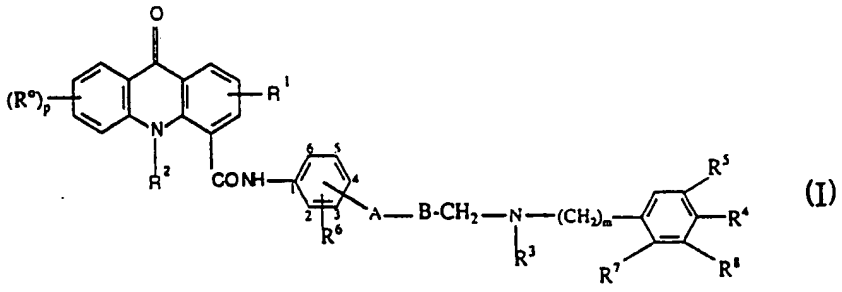
(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU ,SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: ACRIDINE DERIVATIVES



(I)

(57) Abstract

Compounds of general formula (I), wherein A represents an oxygen or a sulphur atom, a bond or a group $(CH_2)_lNR^9$ (where l represents zero or 1 and R^9 represents a hydrogen atom or a methyl group); B represents a C_{1-4}alkylene chain optionally substituted by a hydroxyl group, except that the hydroxyl group and moiety A cannot be attached to the same carbon atom when A represents an oxygen or sulphur atom or a group $(CH_2)_lNR^9$, or when A represents a bond B may also represent a C_{2-4}alkenylene chain; R^3 represents a hydrogen atom or a C_{1-4}alkyl group; m represents 1 or 2; R^7 represents a hydrogen atom or R^3 and R^7 together form a group $-(CH_2)_n-$ where n represents 1 or 2; the novel compounds of formula (I) can sensitize multidrug-resistant cancer cells to chemotherapeutic agents and may be formulated for use in therapy, particularly to improve or increase the efficacy of an antitumour drug.

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ACRIDINE DERIVATIVES

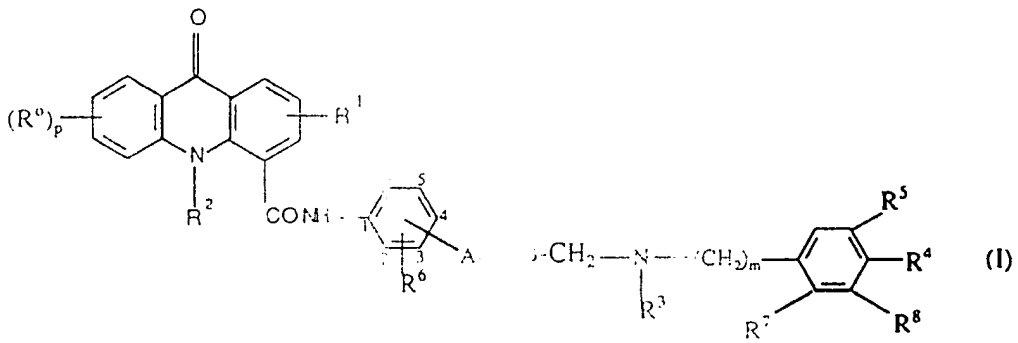
This invention relates to acridine derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to their medical use. In particular it relates to compounds and compositions which are capable of sensitizing multidrug-resistant cancer cells to chemotherapeutic agents.

In many patients, the efficacy of cancer chemotherapy is initially poor or decreases after initial treatment due to the development of resistance to anticancer drugs, known as multidrug-resistance. Multidrug-resistance is a process whereby malignant cells become resistant to structurally diverse chemotherapeutic agents following treatment with a single anti-tumour drug. This acquired drug resistance can be a major clinical obstacle in the treatment of cancer. Some tumours are intrinsically multidrug-resistant, and hence do not respond to chemotherapy.

It has been shown that this type of resistance can be reversed by some calcium channel blockers such as nicardipine and verapamil, by antiarrhythmic agents such as amiodarone and quinidine, as well as by natural products such as cepharanthine. However, these compounds exert their multidrug resistant cell sensitizing activity only at very high doses, well above their intrinsic toxic level, and this severely limits their clinical use in the field of cancer chemotherapy.

A novel group of compounds has now been found which can sensitize multidrug-resistant cancer cells to chemotherapeutic agents at dose levels at which these novel compounds show no toxicity.

Thus, the present invention provides a compound of formula (I):



(I)

wherein R^0 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino or nitro group;

p represents 1; or when R^0 represents C_{1-4}alkoxy may also represent 2 or 3;

R^1 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

A represents an oxygen or a sulphur atom, a bond or a group $(CH_2)_lNR^9$ (where l represents zero or 1 and R^9 represents a hydrogen atom or a methyl group);

B represents a C_{1-4} alkylene chain optionally substituted by a hydroxyl group, except that the hydroxyl group and moiety A cannot be attached to the same carbon atom when A represents an oxygen or sulphur atom or a group $(CH_2)_lNR^9$, or when A represents a bond B may also represent a C_{2-4}alkenylene chain;

R^3 represents a hydrogen atom or a C_{1-4}alkyl group;

m represents 1 or 2;

R^4 represents a hydrogen or a halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

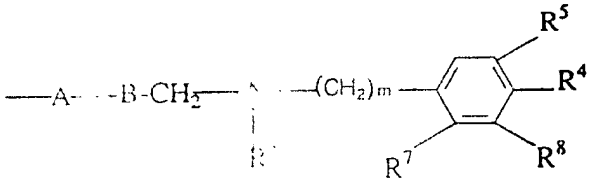
R^5 represents a hydrogen atom or a C_{1-4}alkoxy group;

R^6 represents a hydrogen atom or a C_{1-4}alkyl or C_{1-4}alkoxy group;

R^7 represents a hydrogen atom or R^3 and R^7 together form a group $-(CH_2)_n-$ where n represents 1 or 2;

R^8 represents a hydrogen atom or a C_{1-4}alkoxy group;

the group



is attached at the benzene ring 3 or 4 position relative to the carboxamide substituent, provided that when the group is attached at the benzene ring 3 position then R^6 must be attached at the benzene ring 6 position;

and salts and solvates thereof including physiologically acceptable salts and solvates thereof.

As used herein, an alkyl group, either as such or as part of an alkoxy or alkylthio group may be a straight chain or branched chain alkyl group, for example a methyl, ethyl or prop-2-yl group.

A halogen substituent may be a fluorine, chlorine, bromine or iodine atom.

The group(s) R^0, when other than a hydrogen atom, may be situated at the 5, 6, 7 or 8-position of the acridone molecule, and the group R^1, when other than a hydrogen atom, may be situated at the 1, 2 or 3-position of the acridone molecule.

Examples of the chain -A-B-CH_2- include -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$CH_2NMe(CH_2)_2$-, -CH=CHCH$_2$-, -CH_2CH=CHCH_2-, -CH(OH)CH_2-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$OCH_2CH(OH)CH_2$-, -$NH(CH_2)_2$-, -$S(CH_2)_2$- and -$S(CH_2)_3$-.

A preferred class of compounds of formula (I) is that in which R^0 represents a hydrogen or fluorine atom, or a C_{1-4}alkoxy (e.g. methoxy) group, C_{1-4}alkyl (e.g. methyl) or C_{1-4}alkylthio (e.g methylthio) group, and R^1 is a hydrogen atom. When R^0 represents a substituent other than a hydrogen atom, an R^0 group is preferably situated at the 5-position of the acridone molecule.

Another preferred class of compounds of formula (I) is that in which R^2 represents a hydrogen atom.

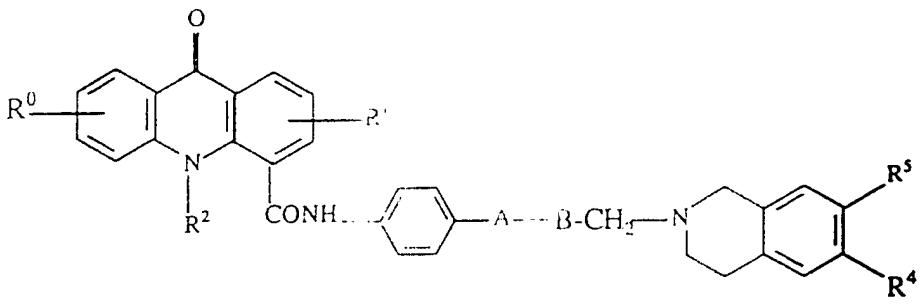
When R^3 represents a hydrogen atom or a C_{1-4}alkyl group, preferably R^3 represents a C_{1-4}alkyl (e.g. methyl) group.

Yet another preferred class of compounds of formula (I) is that in which R^4 represents a hydrogen atom or a C_{1-4}alkoxy (e.g. methoxy) group, R^5 represents a hydrogen atom or a C_{1-4}alkoxy (e.g. methoxy) group and R^8 represents a hydrogen atom or a C_{1-4}alkoxy (e.g methoxy) group, provided that at least one of R^4, R^5 and R^8 represents a C_{1-4}alkoxy (e.g. methoxy) group. A particularly preferred class of compounds of formula (I) is that in which R^4 and R^5 each represent a C_{1-4}alkoxy (e.g. methoxy) group and R^8 represents a hydrogen atom.

A further preferred class of compounds of formula (I) is that in which R^6 represents a hydrogen atom or a methyl, ethyl, methoxy or ethoxy group.

A preferred group of compounds of formula (I) is that in which m represents 1 and R^3 and R^7 together form a group $-(CH_2)_2-$, and physiologically acceptable salts and solvates thereof.

A particular group of compounds of formula (I) is that of formula (Ia)



(Ia)

wherein R^0 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio or nitro group;

R^1 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

A represents an oxygen or a sulphur atom or a bond;

B represents an unsubstituted C_{1-4}alkylene chain;

R^4 and R^5 each independently represents a C_{1-4}alkoxy group; and physiologically acceptable salts and solvates thereof.

A particularly preferred group of compounds of formula (I) is that of formula (Ia) in which R^0 represents a hydrogen or fluorine atom or a C_{1-4}alkoxy (e.g. methoxy) or C_{1-4}alkyl (e.g. methyl) group, R^1 and R^2 each represent a hydrogen atom and R^4 and R^5 each represent a C_{1-4}alkoxy (e.g. methoxy) group. Such compounds in which the R^1 group is situated at the 5-position of the acridone molecule are especially preferred.

It is to be understood that the present invention includes all combinations of the aforementioned particular and preferred groups.

A particularly preferred compound according to the invention is 9,10-dihydro-5-methoxy-9-oxo-N-[4-(2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-

isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide and physiologically acceptable salts and solvates thereof.

Other preferred compounds according to the invention are:-

9,10-dihydro-5-methoxy-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

5-fluoro-9,10-dihydro-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methoxy-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methyl-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methoxy-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-9-oxo-4-acridinecarboxamide;

9,10-dihydro-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-5-methyl-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

Further preferred compounds according to the invention are :-

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]- 9,10-dihydro-5-methoxy-9-oxo-4 acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

Yet further preferred compounds according to the invention are:-

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

Other preferred compounds according to the invention are :-

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[5-[[(3,4-dimethoxyphenyl)methyl]methylamino]pentyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethylamino] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-fluoro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methylthio-9-oxo-4-acridinecarboxamide

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

Yet further preferred compounds according to the invention are :-

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]butyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]- 9,10-dihydro-2-(methylthio)-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propoxy]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with organic or inorganic acids, for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. The solvates may, for example, be hydrates.

Other salts which are not physiologically acceptable may be useful in the preparation of compounds of formula (I) and these form a further part of the invention.

The ability of the compounds of formula (I) to sensitize multidrug-resistant cells has been demonstrated in vitro in the multidrug-resistant Chinese hamster ovary cell line (described by Bech-Hansen et al., J. Cell. Physiol., 1976, 88,23-32) and the multidrug-resistant human mammary carcinoma line (described by Batist et al., (J. Biol. Chem., 1986, 261, 1544-1549) using an assay similar to that described by Carmichael et al., Cancer Research, 1987, 47, 936.

The ability of the compounds of formula (I) to sensitize multidrug-resistant cells has also been demonstrated in vivo in the tumour line P388R (described by Johnson et al., Cancer Treat. Rep., 1978, 6, 1535-1547). The methodology used is similar to that described by Boesch et al., Cancer Research, 1991, 51, 4226-4233. However, in our study the compounds were administered orally, intravenously or intraperitoneally in a single dose.

The present invention accordingly provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy, more particularly for use in the treatment of a mammal, including a human, which is suffering from cancer to :

(a) improve or increase the efficacy of an antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

The present invention also provides a method of treatment of a mammal, including a human, which is suffering from cancer, which method comprises administering to said mammal an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof to :

(a) improve or increase the efficacy of an antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

In another aspect, the present invention provides the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a mammal, including a human, which is suffering from cancer to :

(a) improve or increase the efficacy of an antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

It will be appreciated that the compounds according to the present invention are administered in conjunction with an antitumour drug. Thus, in a further aspect, the present invention provides a product containing a compound of formula (I) or a physiologically acceptable salt or solvate thereof and an antitumour drug as a combined preparation for simultaneous, separate or sequential use in treating cancer, more particularly to :

(a) improve or increase the efficacy of said antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

Examples of suitable antitumour drugs for use in conjunction with compounds of the present invention include Vinca alkaloids (e.g. vincristine, vinblastine and vinorelbine), anthracyclines (e.g. daunorubicin, doxorubicin and aclarubicin), taxol and derivatives thereof (e.g. taxotere), podophyllotoxins (e.g. etoposide and VP16), mitoxantrone, actinomycin, colchicine, gramicidine D, amsacrine or any drug having cross-resistance with the above drugs characterised by the so-called MDR phenotype.

It will be appreciated that if administration of the two drugs is not simultaneous, the delay in administering the second of the active ingredients should not be such as to lose the beneficial effect of the combination.

Thus, in a further aspect, the present invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof and an anticancer

drug in the presence of each other in the human or non-human animal body for use in treating cancer, more particularly to :

(a) improve or increase the efficacy of said antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

Some tumours are often intrinsically multidrug-resistant, notably colon carcinomas, renal cell carcinomas, hepatomas and adrenocortical carcinomas.

Other types of tumour are often initially sensitive but can become multidrug-resistant, notably leukaemias, lymphomas, myelomas, paediatric tumours (e.g. neuroblastomas), sarcomas, and breast, ovarian and lung cancers.

Hence the compounds of the invention are particularly useful in the treatment of mammals, including humans, receiving chemotherapy for one of the above types of cancer.

In using a compound of formula (I), or a physiologically acceptable salt or solvate thereof and an antitumour drug it may be preferable to employ the active ingredients in the form of separate pharmaceutical formulations, although a single combined formulation can be used as demonstrated hereinafter. However, in the latter formulation both active ingredients must of course be stable and mutually compatible in the particular formulation employed.

Pharmaceutical formulations of suitable antitumour drugs and appropriate dosages and dosage rates will generally correspond with those one would use if administering the antitumour drug alone to treat a tumour.

Suitable pharmaceutical formulations and appropriate dosages and dosage rates of compounds of formula (I) and physiologically acceptable salts and solvates thereof are described hereinafter.

Thus, in a further aspect, the invention provides a pharmaceutical composition which comprises a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with one or more physiologically acceptable carriers or excipients.

In another aspect, the present invention provides a pharmaceutical composition which comprises an active amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of a mammal which is suffering from cancer, to:

(a) improve or increase the efficacy of an antitumour drug; or

(b) increase or restore sensitivity of a tumour to an antitumour drug; or

(c) reverse or reduce resistance, whether acquired, induced or inate, of a tumour to an antitumour drug.

The compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration, of which oral and parenteral are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. sodium lauryl sulphate or sodium starch glycolate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

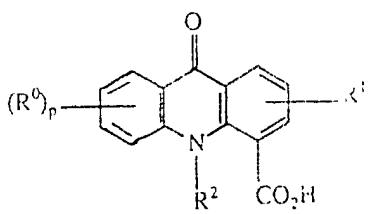
The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily, aqueous or alcoholic vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

A proposed daily dose of the compounds of the invention for administration to a human (of approximately 70kg body weight) is about 10mg to 1000mg, more preferably about 25mg to 500mg. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the route of administration. For example, a daily dose of about 1mg/kg may be appropriate for administration to a human by infusion. The daily dose may be given as a single unit or as two or more subunits administered after appropriate time intervals.

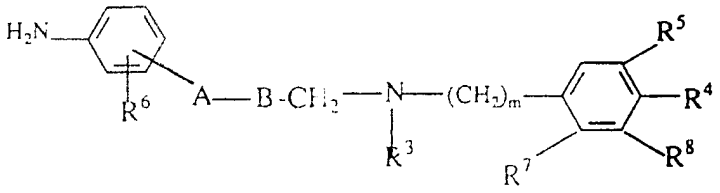
Compounds of general formula (I) and physiologically acceptable salts and solvates thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R^0 to R^5, m, p, A and B are as defined for compounds of formula (I) unless otherwise specified.

Thus according to a first general process (A), a compound of formula (I) may be prepared by reacting a compound of formula (II):



(II)

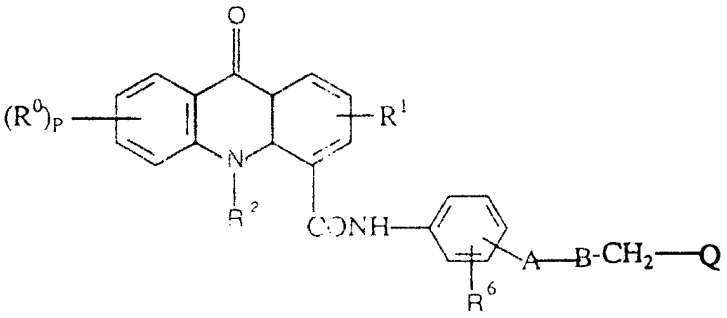
with a compound of formula (III)



(III)

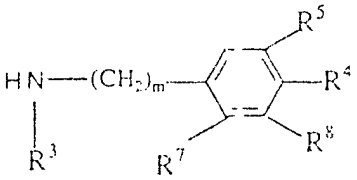
The reaction may be effected using a coupling reagent standardly used in peptide synthesis, such as dicyclohexylcarbodiimide (optionally in the presence of 1-hydroxybenzotriazole), diphenylphosphoryl azide or N,N'- carbonyldiimidazole. The reaction may be conveniently effected in an inert solvent such as an ether (e.g. tetrahydrofuran), a halogenated hydrocarbon (e.g. dichloromethane), an amide (e.g. dimethylformamide) or a ketone (e.g. acetone), and at a temperature of, for example, -10 to +100^{0}C, more preferably at about room temperature.

According to another general process (B), a compound of formula (I) may be prepared by reacting a compound of formula (IV):



(IV)

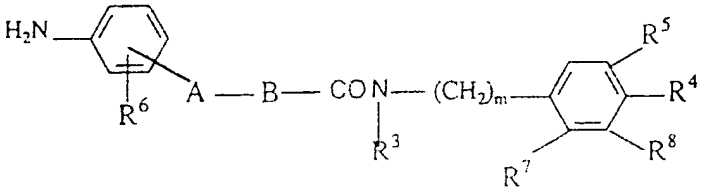
wherein Q represents a halogen (e.g. bromine) atom, with a compound of formula (V):



(V)

or a salt thereof. The reaction may be effected in the presence of an acid acceptor such as an alkali metal carbonate (e.g. potassium carbonate), in the presence or absence of a solvent, at an elevated temperature (e.g. 50 to 120°C). Suitable solvents include ketones (e.g. acetone, methylethylketone or methylisopropylketone) and alcohols (e.g. ethanol or isopropanol).

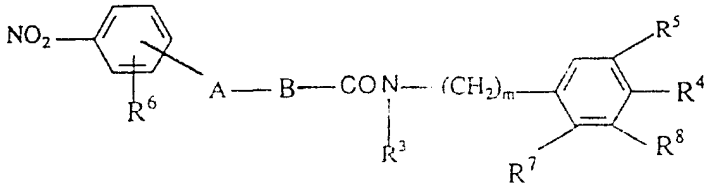
Compounds of formula (III) in which A represents an oxygen atom or a bond may be prepared by the reduction of a compound of formula (VI):



(VI)

(in which A is an oxygen atom or a bond) with a suitable reducing agent such as lithium aluminium hydride in an inert solvent such as an ether (e.g. tetrahydrofuran) at an elevated temperature.

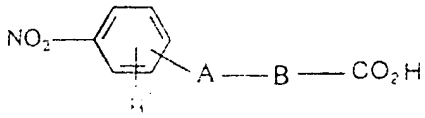
Compounds of formula (VI) may be prepared by the reduction of a compound of formula (VII):



(VII)

by catalytic hydrogenation, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium). The catalyst may be supported on, for example, charcoal. The hydrogenation may be effected in a solvent such as an alcohol (e.g. ethanol), and conveniently at a temperature in the range of 20° to 100°C (e.g. 20° to 50°C) and atmospheric pressure. Alternatively, the reduction may be effected using iron and concentrated hydrochloric acid at an elevated temperature (e.g. reflux). This alternative reduction procedure leaves any double bond present in the compound of formula (VII) intact.

Compounds of formula (VII) may be prepared by the reaction of a compound of formula (VIII):



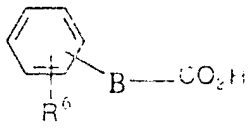
(VIII)

or an activated derivative thereof with a compound of formula (V) as defined previously or a salt thereof, optionally in the presence of a base such as an organic base (e.g. triethylamine or N,N-diisopropylethylamine) or an inorganic base such as an alkali metal carbonate (e.g. potassium carbonate) or hydrogen carbonate (e.g. sodium hydrogen carbonate).

When the free acid (VIII) is reacted with the amine (V), coupling reagents and conditions described in process (A) for the reaction of a compound of formula (II) with a compound of formula (III) may be used.

When an activated derivative of a compound of formula (VIII) is used, this may be, for example, an acid halide (e.g. an acid chloride), prepared by reacting the free acid (VIII) with a halogenating reagent (e.g. thionyl chloride). This activated derivative of a compound of formula (VIII) may be reacted with a compound of formula (V) in a solvent such as acetone in the presence of a base such as sodium hydrogen carbonate.

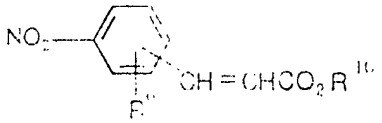
Compounds of formula (VIII) wherein A represents a bond may be prepared by the nitration of a compound of formula (IX):



(IX)

with nitric acid.

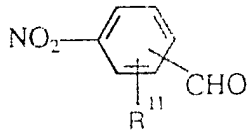
Compounds of formula (VIII) wherein A represents a bond and B represents a group -CH=CH- may conveniently be prepared by the hydrolysis of a compound of formula (X):



(X)

where R^{10} represents a C_{1-4}alkyl group. The hydrolysis may be effected using conventional methods, for example, by using sodium hydroxide in aqueous ethanol.

Compounds of formula (X) may be prepared by the reaction of a compound of formula (XI):



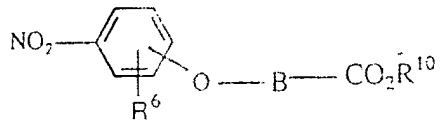
(XI)

where R^{11} represents a hydrogen atom or a C_{1-4}alkyl, C_{1-4}alkoxy or hydroxyl group, with a compound of formula (XII):

$$Ph_3P{=}CHCO_2R^{10} \qquad (XII)$$

where R^{10} is as defined previously, in an inert solvent such as a hydrocarbon (e.g. toluene) and at an elevated temperature. For the preparation of a compound of formula (X) wherein R^6 represents a C_{1-4}alkoxy group from a compound of formula (XI) wherein R^{11} represents a hydroxyl group, the above reaction is followed by alkylation of the hydroxyl group using, for example, an alkyl halide.

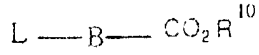
Compounds of formula (VIII) wherein A represents an oxygen atom may be prepared by the hydrolysis of a compound of formula (XIII):



(XIII)

wherein R^{10} is as defined above. The hydrolysis may be effected using conventional methods, for example by using sodium hydroxide in aqueous ethanol.

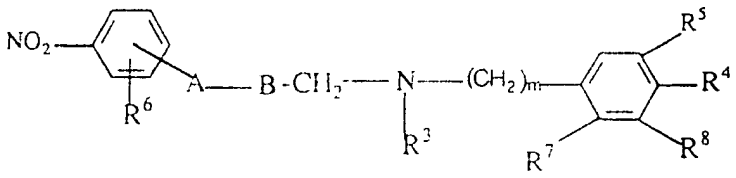
Compounds of formula (XIII) may be prepared by the reaction of a compound of formula (XIV):



(XIV)

wherein L represents a halogen (e.g. bromine) atom, with a nitrophenol derivative in the presence of an alkali metal carbonate (e.g. potassium carbonate), in a solvent such as acetone.

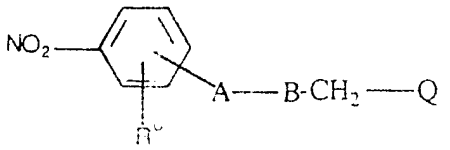
Compounds of formula (III) wherein A represents an oxygen or sulphur atom or a bond may also be prepared by the reduction of a compound of formula (XV):



(XV)

(where A is an oxygen or sulphur atom or a bond) using the conditions described above for the reduction of a compound of formula (VII).

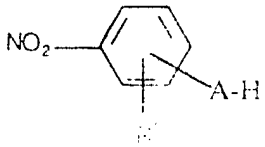
Compounds of formula (XV) may be prepared by heating a compound of formula (XVI):



(XVI)

(wherein Q represents a halogen (e.g. bromine) atom and A is an oxygen or sulphur atom or a bond), with a compound of formula (V) as defined above under the conditions described in process (B) above.

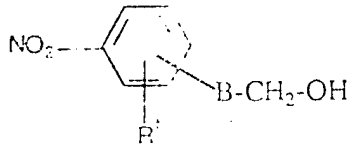
Compounds of formula (XVI) wherein A represents an oxygen or a sulphur atom may be prepared by the reaction of a compound of formula (XVII):



(XVII)

wherein A represents an oxygen or a sulphur atom, with a dihaloalkane Q-B-CH_2-Q in the presence of a suitable base such as an alkali metal carbonate (e.g. potassium carbonate).

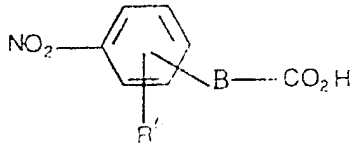
Compounds of formula (XVI) wherein A represents a bond may be prepared by the reaction of a compound of formula (XVIII):



(XVIII)

with an halogenating reagent such as phosphorus tribromide.

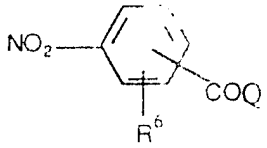
Compounds of formula (XVIII) may be prepared by the reduction of a compound of formula (XIX):



(XIX)

with a suitable reducing agent such as diborane.

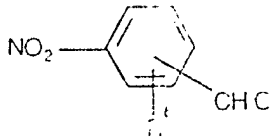
Compounds of formula (XIX) may be prepared by subjecting a compound of formula (XX):



(XX)

wherein Q represents a halogen (e.g. chlorine) atom to one or more successive Arndt-Eistert syntheses (i.e. reaction with diazomethane followed by treatment with, for example, silver oxide and water)

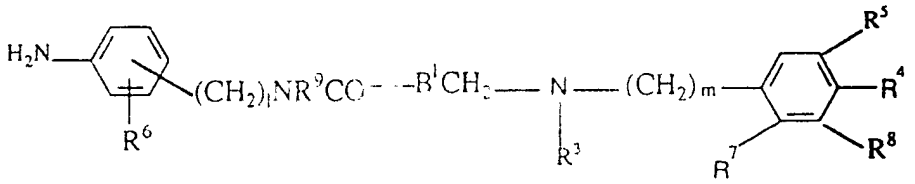
It will be appreciated by one skilled in the art that compounds of formula (XIX) in which B represents an unsubstituted C_{2-4}alkylene chain may also be prepared by subjecting a compound of formula (XXI):



(XXI)

to a Wittig reaction with a suitable phosphorus ylid (e.g. $Ph_3P=CH(CH_2)_3OH$) followed by reduction of the double bond with a suitable reducing agent such as diborane, and oxidation of the primary alcohol to a carboxylic acid with a suitable oxidising agent such as chromium (VI) oxide.

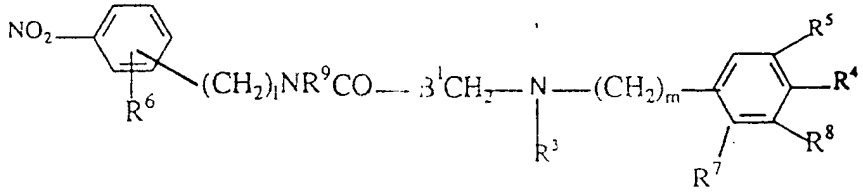
Compounds of formula (III) wherein A represents a group $(CH_2)_1NR^9$ may be prepared by the reduction of a compound of formula (XXII) :



(XXII)

(in which B^1 is a bond or a C_{1-3}alkylene chain optionally substituted by a hydroxyl group) with a suitable reducing agent such as lithium aluminium hydride in an inert solvent such as an ether (e.g. tetrahydrofuran) at an elevated temperature.

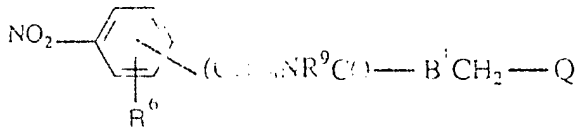
Compounds of formula (XXII) may be prepared by the reduction of a compound of formula (XXIII) :



(XXIII)

by catalytic hydrogenation, for example as described above for preparing compounds of formula (VI).

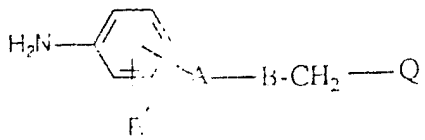
Compounds of formula (XXIII) may be prepared by the reaction of a compound of formula (XXIV) :



(XXIV)

[wherein Q represents a halogen (e.g. chlorine) atom] with a compound of formula (V) as defined previously under the conditions described above in process (B).

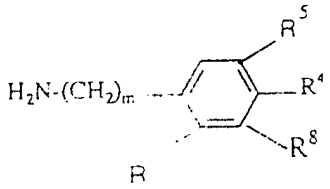
Compounds of formula (IV) may be prepared by the reaction of a compound of formula (II) as defined previously, with a compound of formula (XXV):



(XXV)

wherein Q represents a halogen (e.g. bromine) atom, under the conditions described in process (A) above for the reaction of a compound of formula (II) with a compound of formula (III).

Compounds of formula (V) wherein R^3 represents a C_{1-4}alkyl group may be prepared by reacting a compound of formula (XXVI):



(XXVI)

with benzaldehyde, followed by a C_{1-4}alkyl halide. Hydrolysis of the resultant quaternary salt followed by treatment with dilute sodium hydroxide solution gives a compound of formula (V) wherein R^3 represents a C_{1-4}alkyl group.

It is to be understood that the general procedures above may be used to provide a compound of formula (I) in which B contains a hydroxyl substituent. However, it may be preferable to reduce an intermediate in which B contains an oxo group to provide the desired intermediate in which B contains a hydroxyl substituent at an appropriate stage in the overall procedure.

Intermediates of formulae (III), (IV), (VI), (VII), (VIII), (X), (XIII), (XV), (XVI), (XVIII), (XIX), (XXII) and (XXIII) are novel compounds and represent a further aspect of the present invention.

Compounds of formula (II) are either known, or may be prepared by conventional methods, such as those described by G.W.Rewcastle and W.A.Denny in Synth. Commun., 1985, 217-222.

Compounds of formulae (V), (IX), (XI), (XII), (XIV), (XVII), (XX), (XXI), (XXIV) and (XXVI) are either known, or may be prepared by conventional methods.

Compounds of formula (XXV) are either known or may be prepared by conventional methods. Thus, for example, compounds of formula (XXV) wherein A represents an oxygen atom may be prepared by the reaction of a 4-acetamidophenol derivative with a dihaloalkane Q-BCH_2-Q, followed by acid hydrolysis using, for example, dilute hydrochloric acid.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an aqueous alcohol (e.g. aqueous ethanol), a halogenated hydrocarbon (e.g. dichloromethane), an ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran), or a mixture of two or more of such solvents.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

It will be appreciated that within the above multi-stage processes, the various methods described for the introduction of the desired groups required in the final product may be performed in sequences different from those described. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Intermediates and Examples which are not intended to limit the invention in any way. All temperatures are in ^0C. ^1H NMR spectra were obtained for dilute solutions in $CDCl_3$ unless otherwise stated. Solvents were dried, where indicated, over sodium sulphate. Silica gel used for column chromatography was Merck 60, 230-400 mesh. The following abbreviations are used: THF - tetrahydrofuran; DMF - dimethylformamide.

Intermediate 1

(a) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-(4-nitrophenoxy)propyl] isoquinoline

A mixture of 1-(3-bromopropoxy)-4-nitrobenzene (10g), 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (8.8g) and potassium carbonate (10.6g) in DMF (100ml) was heated at 100° for 16h. The mixture was then filtered and the filtrate evaporated. The residue was taken up in water and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give an oil which crystallised in ether to give the title compound (11.3g), m.p. 100°.

The following compounds were prepared in a similar manner to Intermediate 1(a):

(b) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-[(4-nitrophenyl)thio]-propyl]isoquinoline

The title compound (5.3g) was obtained as an oil (which subsequently crystallised) from 1-[(3-bromopropyl)thio]-4-nitrobenzene (7.0g) and 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (5.8g).
NMR includes d 4.05(6H,s, 2 x OCH_3).

(c) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[2-(4-nitrophenyl)ethyl]- isoquinoline

The title compound (16g) was obtained as a solid from 1-(2-bromoethyl)-4-nitrobenzene (10g) and 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (10.9g). M.p. 118°.
NMR includes d 3.9 (6H,s, 2 x OCH_3).

(d) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[4-(4-nitrophenyl)butyl]- isoquinoline

The title compound (12.6g) was obtained as an oil from 1-(4-bromobutyl)-4-nitrobenzene (12.5g) and 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (11.1g). The product was purified by column chromatography eluting with dichloromethane:methanol (99:1).
NMR includes d 3.85 (6H,s, 2 x OCH_3).

Intermediate 2

(a) 4-[3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy] benzenamine

A solution of Intermediate 1(a) (16g) in ethanol (200ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (1.6g). After hydrogen absorption was completed, the catalyst was filtered off and the solution was concentrated to give the title compound (14.7g) as an oil which crystallised in hexane, m.p. 100^0.

(b) 4-[[3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl) propyl]thio]benzenamine

Intermediate 1(b) (5.3g) was dissolved in a mixture of methanol and concentrated hydrochloric acid (5ml) at room temperature with stirring. Iron powder (3.8g) was then added portionwise, and the mixture was heated under reflux for 1.5h. The mixture was then cooled, poured onto ice, basified with sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated to give the title compound (4.35g) as an oil.

IR: Freq NH_2: 3350cm^{-1}

(c) 4-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]- benzenamine

Intermediate 1(c) (14g) was reduced according to the method of Intermediate 2(b) to give the title compound (12g) as a solid, m.p. 120^0.

(d) 4-[4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)butyl]- benzenamine

Intermediate 1(d) (8.5g) was reduced according to the method of Intermediate 2(a). The product was purified by column chromatography eluting with dichloromethane: methanol (99:1) to give the title compound (4.3g) as an oil which solidified.

IR: Freq NH_2: 3350 cm^{-1}.

Intermediate 3

(a) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(4-nitrophenoxy)acetyl] isoquinoline

A mixture of (4-nitrophenoxy)acetic acid (50g) and thionyl chloride (150ml) was heated under reflux for 3h. The solution was concentrated and then coevaporated with benzene to give 4-nitrophenoxyacetyl chloride as a solid. A solution of this solid (9.4g) in acetone (100ml) was added dropwise to a stirred mixture of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (10g) and sodium hydrogen carbonate (9g) in acetone (100ml) at 0^0. Stirring was continued at room temperature for 16h, the mixture was then filtered, and the filtrate was concentrated. The residue was treated with water and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated to give the title compound (6.6g) as an oil.

IR: Freq CO: 1650cm^{-1}.

The following compound was prepared in a similar manner to Intermediate 3(a).

(b) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-(4-nitrophenyl)-1-oxopropyl]isoquinoline

The title compound (12.3g) was obtained as a solid, m.p. 134^0 from 4-nitrobenzenepropanoic acid (9.75g) and 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (11.6g).

Intermediate 4

(a) 2-[(4-Aminophenoxy)acetyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

Intermediate 3(a) (6.6g) was dissolved in a mixture of methanol (100ml) and concentrated hydrochloric acid (50ml) at room temperature with stirring. Iron powder (5g) was then added portionwise and the mixture was heated under reflux for 3h. The mixture was then cooled, poured onto ice, basified with sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated to give the title compound (4g) as an oil.

IR: Freq NH_2: 3360cm^{-1}.

(b) 2-[3-(4-Aminophenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

A solution of Intermediate 3(b) (12g) in a mixture of ethanol:dioxan (18ml; 5:1) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (1.2g). After hydrogen absorption was completed, the catalyst was filtered off and the solution was concentrated to give the title compound (11g) as a solid.

IR: Freq NH_2: 3360cm^{-1}

Freq CO: 1650cm^{-1}.

Intermediate 5

(a) 4-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethoxy] benzenamine

A solution of Intermediate 4(a) (4g) in THF (50ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.8g) in THF (20ml) at room temperature, and the mixture was heated under reflux for 3h. Water was added carefully to the cooled mixture which was then filtered, washed with THF, evaporated and extracted with dichloromethane. The organic layer was dried and evaporated to give the title compound (1.5g) as an oil.

IR: Freq NH_2: 3350cm^{-1}.

The following compound was prepared in a similar manner to Intermediate 5(a):

(b) 4-[3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl] benzenamine

The title compound (8.6g) was obtained as a solid, m.p. 138^0, by the reduction of Intermediate 4(b) (11g).

Intermediate 6

(a) 1-(3-Bromopropoxy)-3-methoxy-4-nitrobenzene

A mixture of Intermediate 18 (2.4g), 1,3-dibromopropane (7.5ml) and potassium carbonate (2.2g) in DMF (30ml) was stirred at room temperature for 24h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was treated with water and extracted with dichloromethane. The organic extract was then washed with 5% sodium hydroxide solution and brine, dried and concentrated in vacuo to give the title compound (3.5g) as an oil.
NMR includes d 2.3 (2H,m,CH_2), 3.6 (2H,t,CH_2Br), 3.8 (3H,s,OCH_3), 4.1 (2H,t, CH_2O).

The following compounds were prepared in a similar manner to Intermediate 6(a):

(b) 1-(3-Bromopropoxy)-3-methyl-4-nitrobenzene

The title compound (33g) was obtained as an oil from 3-methyl-4-nitrophenol (25g) and 1,3-dibromopropane (83ml).
NMR includes d 2.3 (2H,m,CH_2), 2.5 (3H,s,CH_3), 3.6 (2H,t,CH_2Br), 4.1 (2H,t,OCH_2).

(c) 1-(3-Bromopropoxy)-3-ethyl-4-nitrobenzene

The title compound was obtained from 3-ethyl-4-nitrophenol and 1,3-dibromopropane. NMR includes d 1.23 (t,3H,$\underline{CH_3}$-CH_2-), 2.2 (m,2H,CH_2-$\underline{CH_2}$-CH_2), 2.8 (q,2H,$\underline{CH_2}$-CH_3), 3.5 (t,2H,CH_2Br), 4.1 (t,2H,O-$\underline{CH_2}$-), 6.6 (m,2H,Ar), 7.8 (d,2H,Ar).

Intermediate 7

(a) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-(3-methoxy-4-nitrophenoxy)propyl]isoquinoline

A mixture of Intermediate 6(a) (0.7g), 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (0.4g) and potassium carbonate (0.36g) in DMF (25ml) was heated at 60^0 for 16h. The mixture was filtered and the filtrate was evaporated. The residue was treated with water and extracted with dichloromethane. The organic

layer was dried, concentrated, and the resultant residue was purified by column chromatography eluting with dichloromethane:methanol (99:1) to give the title compound (0.64g) as an oil.

NMR includes d 3.8 (9H,2s, 3 x O[illegible]).

The following compound was prepared in a similar manner to Intermediate 7(a):

(b) 1,2,3,4-Tetrahydro-[illegible]-dimethoxy-2-[3-(3-methyl-4-nitrophenoxy)propyl]isoquinoline

The title compound (5.3g) was obtained as an oil from Intermediate 6(b) (5.7g) and 1,2,3,4- tetrahydro-6,7-dimethoxyisoquinoline (4.0g).

NMR includes d 2.5 (3H,s,CH_3), 3.8 (6H,s, 2 x OCH_3)

Intermediate 8

(a) 2-Methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]benzenamine

A solution of Intermediate 7(a) (0.64g) in ethanol (25ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (60mg). After hydrogen absorption was completed, the catalyst was filtered off and the solution was concentrated in vacuo to give the title compound (0.4g) as a solid.

NMR includes d 3.8 (9H,s, 3 x OCH_3), 3.0 (2H,bs,NH_2).

The following compound was prepared in a similar manner to Intermediate 8(a):

(b) 2-Methyl-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]benzenamine

The title compound (4.8g) was obtained as an oil (which subsequently crystallised) from Intermediate 7(b) (...g).

NMR includes d 2.1 (3H,s,CH_3), 3.8 (6H, s, 2 x OCH_3).

Intermediate 9

(a) 3-Methyl-4-nitrobenzeneacetic acid

3-Methyl-4-nitrobenzoyl chloride (10g) in ether (100ml) was added dropwise to a solution of diazomethane (prepared from 30g of N-methyl-N-nitroso-p-toluene sulphonamide) at 0^0. The reaction mixture was stirred at room temperature for 3h and then concentrated in vacuo to give the diazo ketone as a solid. This diazo ketone in dioxan (100ml) was then added dropwise to a solution of silver oxide in water (prepared from silver nitrate (20g) and dilute sodium hydroxide (100ml)). The mixture was stirred at 75-80^0 for 5 h and filtered. The filtrate was diluted with water, acidified with a solution of nitric acid and the product was extracted with hot diisopropyl ether, treated with brine and concentrated in vacuo to give the title compound (6g) as a solid, m.p. 95^0

In the same way, the following compound was prepared :

(b) 3-Methoxy-4-nitrobenzeneacetic acid, m.p. 130-131^0.

From 3-methoxy-4-nitrobenzoyl chloride.

Intermediate 10

Ethyl 3-(3-hydroxy-4-nitrophenyl)-2-propenoate

To a solution of 3-hydroxy-4-nitrobenzaldehyde (5g) in toluene (50ml) was added carbethoxymethylenetriphenylphosphorane (8.96g), and the mixture was heated under reflux for 2h. The mixture was then concentrated and the residue was purified by column chromatography eluting with cyclohexane:ethyl acetate (6:4) to give the title compound (6.2g) as a solid, m.p. 95^0.

Intermediate 11

Ethyl 3-(3-methoxy-4-nitrophenyl)-2-propenoate

To a solution of Intermediate 9 (5.88g) in DMF (50ml) was added potassium carbonate (4.4g) and methyl iodide (4ml). The mixture was stirred at room temperature for 2h and then concentrated in vacuo. The residue was treated with water and extracted with dichloromethane. The organic extract was dried and concentrated to give the title compound (6.2g) as a solid, m.p. 130^0.

Intermediate 12

3-(3-Methoxy-4-nitrophenyl)-2-propenoic acid

To a suspension of Intermediate 11 (6.2g) in ethanol (50ml) was added a solution of 1N sodium hydroxide (50ml). The mixture was heated under reflux for 1h and then poured onto cracked ice. A solution of 1N hydrochloric acid (60ml) was added and the precipitate was filtered off to give the title compound (4g) as a solid. NMR (DMSO-d_6) includes d 3.95 (3H,s,OCH_3).

Intermediate 13

3-(3-Ethoxy-4-nitrophenyl)-2-propenoic acid

Using reactions similar to those described in Intermediates 11 and 12, the title compound (3.1g) was obtained as a solid, m.p. 272^0, from Intermediate 10 (4.0g), ethyl iodide (4ml) and potassium carbonate (2.6g), followed by saponification of the ester function.

Intermediate 14

(a) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-(3-methoxy-4-nitrophenyl)-1-oxo-2-propenyl]isoquinoline

A mixture of Intermediate 12 (4.9g) and 1-hydroxybenzotriazole (2.95g) in DMF (100ml) was stirred at room temperature for 10 min. 1,2,3,4-Tetrahydro-6,7 dimethoxy-isoquinoline (5g) was added, followed by dicyclohexylcarbodiimide (4.52g) and the mixture was stirred at room temperature for 16h and then filtered. The filtrate was concentrated in vacuo, treated with dilute hydrochloric acid, then dilute sodium hydroxide solution and extracted with dichloromethane. The organic extract was dried, concentrated in vacuo, and the residue was purified by column

chromatography eluting firstly with ethyl acetate:cyclohexane (4:6), then with ethyl acetate to give the title compound which was crystallised from ethyl acetate/ether and obtained as crystals (6.5g).

NMR includes d 3.85 (6H,s, 2 x OCH$_3$), 3.95 (3H,s,OCH$_3$).

The following compounds were prepared in a similar manner to Intermediate 14(a):

(b) 2-[3-(3-Ethoxy-4-nitrophenyl)-1-oxo-2-propenyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

The title compound (5.3g) was obtained as a solid, m.p. 152^0 from Intermediate 13 (3.0g) and 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (2.5g).

(c) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[(3-methyl-4-nitrophenyl)acetyl]isoquinoline

The title compound (2.8g) was obtained as an oil from Intermediate 9(a) (1.8g) and 1,2,3,4-tetrahydro-6,7-dimethoxy- isoquinoline (1.9g).

IR: Freq CO: 1650cm^{-1}.

Intermediate 15

(a) 2-[3-(4-Amino-3-methoxyphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

A solution of Intermediate 14(a) (6.5g) in methanol/ethyl acetate (1:1; 100ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (0.3g). After hydrogen absorption was completed, the catalyst was filtered off and the solution was concentrated in vacuo to give the title compound (6g) as an oil.

NMR includes d 3.8 (9H,s, 3 x OCH$_3$).

The following compounds were prepared in a similar manner to Intermediate 15(a):

(b) 2-[3-(4-Amino-3-ethoxyphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

The title compound (4.5g) was obtained as an oil from Intermediate 14(b) (5.3g).

IR: Freq CO : 1640cm^{-1}

Freq NH_2: 3450cm^{-1}.

(c) 2-[(4-Amino-3-methylphenyl)acetyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

The title compound (2.4g) was obtained as an oil from Intermediate 14(c) (2.8g).

IR: Freq CO : 1650cm^{-1}

Freq NH_2: 3340-3440cm^{-1}.

Intermediate 16

(a) 2-Methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]benzenamine

A solution of Intermediate 14(a) (6g) in THF (30ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.84g) in THF (50ml) at room temperature, and the mixture was heated under reflux for 2h. Water was carefully added to the cooled mixture which was then filtered. The filtrate was concentrated in vacuo, treated with water and extracted with dichloromethane. The organic layer was dried and concentrated in vacuo to give the title compound (4.2g) as an oil.

IR: Freq NH_2 : 3340-3440cm^{-1}.

The following compounds were prepared in a similar manner to Intermediate 16(a):

(b) 2-Ethoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]benzenamine

The title compound (2.5g) was obtained as an oil from Intermediate 15(b) (4.5g).

IR: Freq NH_2 : 3340-3440cm^{-1}.

(c) 2-Methyl-4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]benzenamine

The title compound (1.7g) was obtained as a solid, m.p. 105^0, from Intermediate 15(c) (2.4g).

Intermediate 17

3-Chloro 4-nitrophenol

Concentrated nitric acid (10ml) in acetic acid (30ml) was added dropwise to a cooled solution of 3-chlorophenol (10g) in acetic acid (10ml). After 1 hour at -5^0, the mixture was poured onto ice, extracted with ether, dried over sodium sulfate and evaporated. The residue was then purified by column chromatography eluting with hexane-ethyl acetate (85:15) to give the title compound (9g). M.p. 120^0.

Intermediate 18

3-Methoxy-4-nitrophenol

A solution of Intermediate 17 (4.4g) in methanol (15ml) was added to a solution of sodium (5.8g) in methanol (60ml) and the mixture was stirred in an autoclave for 16 h at 100^0. The mixture was cooled and poured onto ice and acidified with concentrated hydrochloric acid. Methanol was then evaporated in vacuo inducing the crystallisation of the title compound (3.5g). M.p. 142^0.

Intermediate 19

1-(2-Chloroethoxy)-3-methyl-4-nitrobenzene

A mixture of 3-methyl-4-nitrophenol (10g), 1-bromo-2-chloroethane (16ml) and sodium hydroxide (2.9g) in water (50 ml) was stirred under reflux for 16h. The mixture was diluted with water and the product was extracted with methylene chloride. The organic extract was dried on sodium sulfate and concentrated in vacuo

to give the title compound as an oi .81g). NMR includes d 2.5 (s,3H,-CH_3), 3.9 (t,2H,CH_2-O) and 4.3 (t,2H,-CH_2-O).

Intermediate 20

(a) 3,4-Dimethoxy-N-methylbenzeethanamine

3,4-Dimethoxybenzeneeth mine (100g, was mixed with benzaldehyde (59g), and rotoevaporated to give an oil. Methyl iodide (69 ml) was then added and the mixture was heated for 48h at 40° and then boiled with 80% ethanol (500ml) for 3h. After half of the ethanol had evaporated, the solution was treated with ether (1 litre) to give a solid that was filtered washed with ether, treated with dilute sodium hydroxide and extracted with ether to give the title compound (80g) as an oil that was distilled under reduced pressure, b.p. 0.1mm; 92-95°.

(b) 3,4-Dimethoxy-N-methylbenzenemethanamine

3,4-Dimethoxybenzenemeth mine (100 g) was mixed with benzaldehyde (64g), and rotoevaporated to give a il. Methyl iodide (75 ml) was then added and the mixture was heated for 48h at 40° and then boiled with 80% ethanol (800 ml) for 3h. After half of the ethanol had ev orated, the solution was treated with ether (1 litre) to give a solid that was filtered washed with ether, treated with dilute sodium hydroxide and extracted with ether to give the title compound (69g) as an oil that was distilled under reduced pressure, b.p. 0.03mm; 91°.

The following amines were prepared in a similar manner to Intermediates 20(a) and 20(b):

(c) 4-Fluoro-N-methylbenzenemethanamine as an oil; IR includes a peak at 3300cm (NH).

From 4-fluorobenzenemethan ne and methyl iodide.

(d) 4-Methoxy-N-methylbenzenemethanamine as an oil; IR includes a peak at 3310cm^{-1} (NH).

From 4-methoxybenzenemethanamine and methyl iodide.

(e) 4-Methoxy-N-methylbenzeneethanamine as an oil; IR includes a peak at 3310cm^{-1} (NH).

From 4-methoxybenzeneethanamine and methyl iodide.

(f) 4-(Methylthio)-N-methylbenzeneethanamine as an oil; IR includes a peak at 3310cm^{-1} (NH).

From 4-(methylthio)benzenemethanamine and methyl iodide.

(g) 4-Methyl-N-Methylbenzenemethanamine as an oil: IR includes a peak at 3310cm^{-1} (NH).

From 4-methylbenzenemethanamine and methyl iodide.

Intermediate 21

(a) 3,4-Dimethoxy-N-methyl-N-[3-(3-methyl-4-nitrophenoxy)propyl] benzenemethanamine

A mixture of Intermediate 6(b) (5g), Intermediate 20(b) (4g) and potassium carbonate (3.3g) in DMF (80ml) was heated at 60^0 for 36h. The mixture was filtered and the filtrate was evaporated. The residue was added to water and extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate filtered and evaporated. The oily residue was then chromatographed with dichloromethane/methanol (99:1) to give the title compound as an oil (4.6 g). NMR includes d 2.2 (s,3H,-CH_3), 2.4 (s,3H,-CH_3) and 3.8 (s,6H,2OCH_3).

In the same way, the following compounds were prepared :

(b) 3,4-Dimethoxy-N-[3-(3-methoxy-4-nitrophenoxy)propyl]-N-methyl-benzenemethanamine as an oil

From Intermediate 6(a) and Intermediate 20(b). NMR includes d 2.2 (s,3H,N-CH_3) and 3.85 - 3.9 (2s,3H-6H,3O-CH$_3$).

(c) 3,4-Dimethoxy-N-[3-(3-...yl-4-nitrophenoxy)propyl]-N-methyl-benzenemethanamine as an oil.

From Intermediate 6(c) and Intermediate 20(b). NMR includes d 2.2 (s,3H,N-CH_3) and 3.85 - 3.9 (s,6H,20-CH_3)

(d) 3,4-Dimethoxy-N-methyl-N-[2-(3-methyl-4-nitrophenoxy)ethyl] benzenemethanamine as an oil

From Intermediate 19 and Intermediate 20(b). NMR includes d 2.3 (s,3H,N-CH_3), 2.5 (s,3H,N-CH_3) and 3.8 (s,6H,2-OCH_3).

Intermediate 22

(a) N-[3-(4-Amino-3-methylphenoxy)propyl]-3,4-dimethoxy-N-methylbenzenemethanamine

A solution of Intermediate 21 (4.6g) in ethanol (100ml) was hydrogenated at room temperature in presence of 5% palladium-on- carbon 10% (450mg). After the hydrogen absorption was complete, the catalyst was filtered off and the solution concentrated to give the title compound (3.7g) as an oil. NMR includes d 2.0 (s,3H,CH_3), 2.1 (s,3H,N-CH_3) and 3.7 (s,6H,2OCH_3).

In the same way, the following compounds were prepared :

(b) N-[3-(4-Amino-3-methoxyphenoxy)propyl]-3,4-dimethoxy-N-methylbenzenemethanamine as an oil.

From Intermediate 21(b). NMR includes d 2.2 (s,3H,N-CH_3),3.85-3.9 (s,3H,OCH_3) and 3.9 (s,6H,2OCH_3)

(c) N-[3-(4-Amino-3-ethylphenoxy)propyl]-3,4 dimethoxy-N-methylbenzenemethanamine as an oil

From Intermediate 21(c). NMR includes d 2.1 (s,3H,N-CH_3) and 3.7 (s,6H,2OCH_3).

(d) N-[2-(4-Amino-3-methylphenoxy)ethyl]-3,4-dimethoxy-N-methylbenzenemethanamine as an oil

From Intermediate 21(d). NMR includes d 2.0 (s,3H,N-CH_3), 2.2 (s,3H,N-CH_3) and 3.8 (s,6H,2OCH_3).

Intermediate 23

Diethyl (3-methyl-4-nitrobenzyl)malonate

To a solution of sodium ethanolate [prepared from 1.35g Na in ethanol (30ml)] were added diethyl malonate (9.2ml) and then dropwise 3-methyl-4-nitrobenzyl bromide (13.4g). The mixture was stirred 30 minutes at room temperature, then 30 minutes under reflux and then concentrated. The residue is treated with water and hexane, the precipitate filtered and the filtrate extracted with diethyl ether. The organic extract was dried on sodium sulfate and concentrate to give the title compound as an oil (4g).

NMR includes d 1.15 (t,6H,2xCH_3-CH_2), 2.5 (s,3H,CH_3-Ar), 3.16 (s,2H,CH_2-Ar), 4.0 (q,4H,2xCH_2-CH_3), 7.0 (m,2H,Ar), 7.7 (d,1H,Ar).

Intermediate 24

3-(3-Methyl-4-nitrophenyl)propionic acid

Intermediate 23 (4g) was added dropwise to a solution of potassium hydroxide (3.1g) in water and the mixture is stirred under reflux for 2 hours, diluted with water, washed with diethyl ether and then acidified with a dilute solution of hydrochloric acid. After extraction with diethyl ether and concentration, the concentrate was heated at 130^0 for 3h to give the title compound as a yellow solid (2.3g). NMR ($CDCl_3$) includes d 2.5 (s,3H,CH_3) and 2.9 (m,4H,2CH_2).

Intermediate 25

(a) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-3-methyl-4-nitrobenzeneethanamide

A mixture of Intermediate 9(a) (2g) and 1-hydroxybenzotriazole (1.6g) in DMF (35ml) was stirred at room temperature for 5 min. Intermediate 20(b) (1.9g) in

DMF (:0 ml) was then added, follc :d by dicyclohexylcarbodiimide (2.1g) and the mixtur was stirred at room tempe ure for 16h and then filtered. The filtrate was concentrated in vacuo, treated wit dilute sodium hydroxide solution and extracted with di hloromethane. The combi l. dried organic extracts were evaporated and the residue was purified b olumn chromatography eluting with dichloromethane/methanol (97:3) give the title compound (1.7g) as an oil. IR includes a signal at 1640cm-1 (CO,

In the same way, the followin ompounds were prepared :

(b) N-[(3,4-Dimethoxyphe yl)methyl]-N-methyl-3-methoxy-4-nitrobenzeneethanamide

From Intermediate 9(b) and ntermediate 20(b). IR includes a signal at 1645cm 1 (CO).

(c) N-[(3,4-Dimethoxyphe yl)methyl]-N-methyl-3-methyl-4-nitrobenzenepropanamide as an oil

From Intermediate 24 and Inte mediate 20(b). NMR ($CDCl_3$) includes d 2.5 (s,3H,-CH_3), 2.9 (s.3H,N-CH_3) and (s,6H,2OCH_3).

Intermediate 26

(a) 4-Amino-3-methyl-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzeneethanamide

A solution of Intermediate 25 (1.7g) in ethanol (60ml) was hydrogenated at room temperature in presence of % palladium-on- carbon (0.25g). After the hydrogen absorption was complete the catalyst was filtered off and the solution concentrated to give the title compo (1.4g) as an oil. IR includes signals at 3450-3350 cm 1 (NH_2) and 1630 cm-1 (C

In the same way, the following ompounds were prepared :

(b) 4-Amino-3-methoxy-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzeneethanamide

From Intermediate 25(b). IR includes signals at 3450-3350cm-1 (NH_2) and 1625 cm-1 (CO).

(c) 4-Amino-3-methyl-N-[(3,4-dimethoxyphenyl)methyl]-N-methyl-benzenepropanamide

From Intermediate 25(c). NMR includes d 2.1 (3H,s,CH_3), 2.75 (3H,s,N-CH_3) and 3.8 (6H,s,2OCH_3).

Intermediate 27

(a) 4-Amino-3-methyl-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzeneethanamine

A solution of Intermediate 26(5.4g) in THF (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.7g) in THF (30 ml) at room temperature and the mixture was heated under reflux for 3h. Water was added carefully to the cooled mixture which was then filtered on a celite pad, washed with THF, evaporated and extracted with ether. The ethereal extracts were dried and evaporated to give the title compound (4g) as an oil. IR includes a signal at 3450 - 3350 cm-1 (NH_2).

In the same way, the following compounds were prepared :

(b) 4-Amino-3-methoxy-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzeneethanamine

From Intermediate 26(b). IR includes a signal at 3455 - 3345 cm-1 (NH_2).

(c) 4-Amino-3-methyl-N-[(3,4-dimethoxyphenyl)methyl]-N-methyl-benzenepropanamine as an oil

From Intermediate 26(c). NMR includes d 2.0 (3H,s,-CH_3), 2.1 (3H,s,N-CH_3) and 3.8 (6H,s,2OCH_3).

Intermediate 28

N-[(3,4-Dimethoxyphenyl)meth]-N-methyl-3-methoxy-4-nitrobenzene-2-propenamide

A mixture of Intermediate 1 (3g) and 1-hydroxybenzotriazole (1.95g) in DMF (100 ml) was stirred at room temperature for 10 minutes. Intermediate 20(b) (2.5g) was added, followed by dicyclohexylcarbodiimide (2.95g) and the mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, treated with dilute hydrochloric acid solution, then dilute sodium hydroxide solution and extracted with methylene chloride. The organic extract was dried with sodium sulfate and concentrated. The residue was purified by column chromatography eluting with ethyl acetate to give the title compound (4.4g). NMR includes d 2.9 (3H,s,N-CH_3), 3.85 (3H,s,OCH_3) and 3.9 (6H,s,2OCH_3).

Intermediate 29

4-Amino-3-methoxy-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzenepropanamide

A solution of Intermediate 28 (8.4g) in methanol/ethyl acetate (1:1, 100ml) was hydrogenated at room temperature in presence of 10% palladium-on-carbon (0.3g). After the hydrogen absorption was completed, the catalyst was filtered off and the solution concentrated to give the title compound (7.3g) as an oil. IR includes signals at 3450-3350 cm-1 (NH_2) and 1635 cm-1 (CO).

Intermediate 30

4-Amino-3-methoxy-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzenepropanamine

A solution of Intermediate 29 (7.32g) in tetrahydrofuran (100 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.3g) in tetrahydrofuran (100 ml) at room temperature and the mixture was heated under reflux 1 h. Water (20 ml) was added carefully to the cooled mixture which was filtered on a celite pad, washed with diethyl ether, concentrated and extracted with

methylene chloride. The organic extract was dried on sodium sulfate, evaporated and the product purified by column chromatography on silica gel eluting with dichloromethane/methanol (95:5) to give the title compound as an oil (2.5g). IR includes a signal at 3440-3340 cm-1 (NH_2).

Intermediate 31

(a) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-4-nitrobenzenebutanamide

A mixture of 4-nitrobenzenebutanoic acid (31 g) and thionyl chloride (200 ml) was heated under reflux for 1h. The solution was then concentrated and coevaporated with benzene to give an oil. This oil was dissolved in acetone (100 ml) and added dropwise to a stirred mixture of Intermediate 20(b) (28.6g) and sodium hydrogen carbonate (35 g) in acetone (150 ml) at room temperature. Stirring was continued for 4h, the mixture was then filtered and the filtrate was concentrated. The residue was poured into water and then extracted with dichloromethane. The organic phase was evaporated to give the title compound (41.5 g) as an oil. Recrystallisation from ethanol gave the title compound as a solid, MP : 90°.

(b) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-4-nitrobenzeneethanamide

A mixture of 4-nitrobenzeneacetic acid (22 g) and thionyl chloride (100 ml) was heated under reflux for 3h. The solution was concentrated and then coevaporated with benzene to give an oil. This oil was dissolved in acetone (100 ml) and added dropwise to a stirred mixture of Intermediate 20(b) (22g) and sodium hydrogen carbonate (15.3 g) in acetone (100 ml) at room temperature. Stirring was continued for 6 hours, the mixture was then filtered and the filtrate was concentrated. The residue was poured into water and extracted with ethyl acetate. The organic phase was washed first with dilute sodium hydroxide solution, then with water, dried and concentrated to give the title compound (22.3g) as an oil. IR includes a peak at 1650cm-1 (CO).

The following amides were prepared in a similar manner to Intermediates 31(a) and 31(b) :

(c) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-4-nitrobenzenebutanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenebutanoic acid and Intermediate 20(a).

(d) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-4-nitrobenzenepropanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenepropanoic acid and Intermediate 20(a).

(e) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-4-nitrobenzeneethanamide as an oil; IR includes a peak at 1650cm^{-1} (CO).

From 4-nitrobenzeneacetic acid and Intermediate 20(a).

(f) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-4-nitrobenzenepropanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenepropanoic acid and Intermediate 20(b).

(g) N-[(4-Methoxyphenyl)methyl]-N-methyl-4-nitrobenzenepropanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenepropanoic acid and Intermediate 20(d).

(h) N-[2-(4-Methoxyphenyl)ethyl]-N-methyl-4-nitrobenzenebutanamide as an oil; IR includes a peak at 1650cm^{-1} (CO).

From 4-nitrobenzenebutanoic acid and Intermediate 20(e)

(i) N-[(4-Fluorophenyl)methyl]-N-methyl-4-nitrobenzenebutanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenebutanoic acid and Intermediate 20(c).

(j) N-[[4-(Methylthio)phenyl]methyl]-N-methyl-4-nitrobenzenebutanamide as an oil; IR includes a peak at 1640cm^{-1} (CO).

From 4-nitrobenzenebutanoic acid and Intermediate 20(f).

(k) N-[2-(4-Methoxyphenyl)ethyl]- methyl-4-nitrobenzeneethanamide an oil; IR includes a peak at 1650cm^{-1} (CO).

From 4-nitrobenzeneacetic acid and Intermediate 20(e).

(l) N-[(3,4-Dimethoxyphenyl)meth yl]-N-methyl-4-nitrobenzenepentan nide as an oil, IR includes a peak at 1650cm^{-1} (CO).

From 4-nitrobenzenepentanoic acid and Intermediate 20(b).

Intermediate 32

(a) 4-Amino-N-[(3,4-dimethoxyphe yl)methyl]-N-methylbenzenebutana ide

Intermediate 31(a) (40g) was di solved in a mixture of methanol (30 ml) and concentrated hydrochloric acid (160 ml) at room temperature with stirr g. Iron powder (21 g) was then added slowly, and the reaction mixture was hea d under reflux for 1h. The mixture was then evaporated and basified with sodium h droxide solution. Ethyl acetate (1 litre) was added and the mixture was filtered. The organic phase was washed with water, dried and evaporated to give the title comp nd (30 g) as an oil. IR includes peaks at 1630 cm^{-1} (CO), 3350-3430cm-1 (NH_2).

(b) 4-Amino-N-[(3,4-dimethoxyphe yl)methyl]-N-methylbenzeneethana ide

Intermediate 31(b) (22g) was dissolved in a mixture of methanol (30 ml) and concentrated hydrochloric acid (150 ml) at room temperature with stirr g. Iron powder (18 g) was then added slowly, and the reaction mixture was hea d under reflux for 3 h. The mixture was then evaporated, basified with sodium h droxide solution, and extracted with ethyl a etate. The organic phase was was d with water, dried and evaporated to give the title compound (14 g) as an oil. IR includes peaks at 1620cm-1 (CO) and 3350-3430cm-1 (NH_2).

The following compounds were prepared in a similar manner to Inte ediates 32(a) and 32(b) :

(c) 4-Amino-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylbenzenebutanamide as an oil; IR includes peaks at 1630cm^{-1} (CO) and 3330-3420cm^{-1} (NH_2).

From Intermediate 31(c).

(d) 4-Amino-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylbenzenepropanamide as an oil; IR includes peaks at 1630cm^{-1} (CO) and 3340-3420cm^{-1} (NH_2).

From Intermediate 31(d).

(e) 4-Amino-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylbenzeneethanamide as an oil; IR includes peaks at 1640cm^{-1} (CO) and 3330-3420cm^{-1} (NH_2).

From Intermediate 31(e).

(f) 4-Amino-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzenepropanamide as an oil; IR includes peaks at 1640cm^{-1} (CO) and 3350-3440cm^{-1} (NH_2).

From Intermediate 31(f).

(g) 4-Amino-N-[(4-methoxyphenyl)methyl]-N-methylbenzenepropanamide as an oil; IR includes peaks at 1650cm^{-1} (CO) and 3330-3420cm^{-1} (NH_2).

From Intermediate 31(g).

(h) 4-Amino-N-[2-(4-methoxyphenyl)ethyl]-N-methylbenzenebutanamide as an oil; IR includes peaks at 1640cm^{-1} (CO) and 3340-3430cm^{-1} (NH_2).

From Intermediate 31(h).

(i) 4-Amino-N-[(4-fluorophenyl)methyl]-N-methylbenzenebutanamide as an oil; IR includes peaks at 1640cm^{-1} (CO) and 3340-3430cm^{-1} (NH_2).

From Intermediate 31(i).

(j) 4-Amino-N-[[4-(methylthio)phenyl]methyl]-N-methylbenzenebutanamide as an oil; IR includes peaks at 1640cm^{-1} (CO) and 3340-3430cm^{-1} (NH_2).

From Intermediate 31(j).

(i) 4-Amino-N-[2-(4-methoxyphe yl)ethyl]-N-methylbenze neethanan le as an oil; IR includes peaks at 1635cm^{-1} (C) and 3340-3440cm^{-1} (NH_2).

From Intermediate 31(k).

(l) 4-Amino-N-[(3,4-dimethoxyphe nyl)methyl]-N-methylben zenepentan nide as an oil; IR includes peaks at 1630cm^{-1} (CO) and 3340-3420cm^{-1} (NH_2).

From Intermediate 31(l).

Intermediate 33

(a) 4-Amino-N-[(3,4-dimethoxyphe nyl)methyl]-N-methylben zenebutana ine

A solution of Intermediate 32(a) (30g) in THF (150 ml) was added dropwise to a stirred suspension of lithium alum nium hydride (10 g) in THF (150 ml) at room temperature and the mixture was heated under reflux for 3h. Water was added carefully to the cooled mixture, which was then filtered, washed with THF, evaporated, and extracted with ether. The combined ethereal extracts were dried and evaporated to give the title compound (21 g) as an oil. IR includes a peak at 3370-3440cm-1 (NH_2).

(b) 4-Amino-N-[(3,4-dimethoxyphe nyl)methyl]-N-methylben zeneethan ine

A solution of Intermediate 32(b) (14g) in THF (100 ml) was added dropwise to a stirred suspension of lithium alum nium hydride (8 g) in THF (100 ml) at room temperature and the mixture was heated under reflux for 3 hours. Water was added carefully to the cooled mixture which was then filtered, washed with THF, evaporated and extracted with ether. The combined ethereal extracts were dried and evaporated to give the title compound (9.5 g) as an oil. IR includes a peak at 3360-3430cm-1 (NH_2).

The following compounds were prepared in a similar manner to Intermediates 33(a) and 33(b) :

(c) 4-Amino-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylbenzenebu namine as an oil; IR includes a peak at 3360-3430cm^{-1} (NH_2).

From Intermediate 32(c).

(d) 4-Amino-N-[2-(3,4-dimethox phenyl)ethyl]-N-methylbenzenepro namine as an oil; IR includes a peak at 3360-3460cm^{-1} (NH_2).

From Intermediate 32(d).

(e) 4-Amino-N-[2-(3,4-dimethox phenyl)ethyl]-N-methylbenzeneeth namine as an oil; IR includes a peak at 3360-34 0cm^{-1} (NH_2).

From Intermediate 32(e).

(f) 4-Amino-N-[(3,4-dimethoxyph enyl)methyl]-N-methylbenzeneprop namine as an oil; IR includes a peak at 3360-34 0cm^{-1} (NH_2).

From Intermediate 32(f).

(g) 4-Amino-N-[(4-methoxyphen)methyl]-N-methylbenzenepropan nine as an oil; IR includes a peak at 3360-3430c n^{-1} (NH_2).

From Intermediate 32(g).

(h) 4-Amino-N-[2-(4-methoxyph nyl)ethyl]-N-methylbenzenebutanam nine as an oil; IR includes a peak at 3380-3460c n^{-1} (NH_2).

From Intermediate 32(h).

(i) 4-Amino-N-[(4-fluorophenyl) ethyl]-N-methylbenzenebutanamine as an oil; IR includes a peak at 33.0- 430cm^{-1} (NH_2).

From Intermediate 32(i).

(j) 4-Amino-N-[[4-(methylthio)ph enyl]methyl]-N-meth b zenebut namine as an oil; IR includes a peak at 3350-34 0cm^{-1} (NH_2)

From Intermediate 32(j).

(k) 4-Amino-N-[2-(4-methoxyphenyl)ethyl]-N-methylbenzeneethanam e as an o..; IR includes a peak at 3360-3440cm^{-1} (NH_2).

From Intermediate 32(k).

(l) 4-Amino-N-[(3,4-dimethoxyphe..yl)methyl]-N-methylbenzenepentan nine as an oil; IR includes a peak at 3360-3440cm^{-1} (NH_2).

From Intermediate 32(l).

Intermediate 34

(a) N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-2-(4-nitrophenoxy)acet nide

A mixture of (4-nitrophenoxy)..cetic acid (51 g) and thionyl chlo. de was heated under reflux for 2h. The solut..n was concentrated and then coevaporated with benzene to give a solid. This s lid was dissolved in acetone (250 ml) and added dropwise to a stirred mixture of Intermediate 20(a) (50g) and sodium hydrogen carbonate (22g) in acetone (250 ml) at room temperature. Stirring was continued for 4h, the mixture was then filtered and the filtrate was concentrated. The residue was treated with water and extracted with ethyl acetate. The organic phase was washed first with dilute sodium hydroxide, then with water, dried and concentrated. Recrystallisation from ethanol gave the title compound (.. g). MP 121°.

The following compounds were prepared in a similar manner to Intermediate 34(a):

(b) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-2-(4-nitrophenoxy)a. tamide. MP 130°

From (4-nitrophenoxy)acetic acid and Intermediate 20(b).

(c) N-Methyl-2-(4-nitrophenoxy)-N-(phenylmethyl)acetamide MP 98°.

From (4-nitrophenoxy)acetic acid and N-methylbenzenemethanamine.

(d) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-2-(4-nitrophenylthio)acetamide as an oil. NMR includes signals at δ 3.0 (3H,s,N-CH_3) and 3.8 (6H,s,O-CH_3).

From (4-nitrophenylthio)acetic acid and Intermediate 20(d).

(e) N-[2-(4-Methoxyphenyl)ethyl]-N-methyl-2-(4-nitrophenoxy)acetamide. **MP** 107°.

From (4-nitrophenoxy)acetic acid and Intermediate 20(e)

(f) N-[(4-Methoxyphenyl)methyl]-N-methyl-2-(4-nitrophenoxy)acetamide. **MP** 120°.

From (4-nitrophenoxy)acetic acid and Intermediate 20(d)

(g) N-Methyl-N-[(4-methylphenyl)methyl]-2-(4-nitrophenoxy)acetamide. **MP** 126°.

From (4-nitrophenoxy)acetic acid and Intermediate 20(g)

(h) N-Methyl-N-[[4-(methylthio)phenyl]methyl]-2-(4-nitrophenoxy)acetamide. MP 122°.

From (4-nitrophenoxy)acetic acid and Intermediate 20(f).

(i) N-Ethyl-2-(4-nitrophenoxy)-N-(phenylmethyl)acetamide as an oil; it includes a peak at 1655cm^{-1} (CO).

From (4-nitrophenoxy)acetic acid and N-ethylbenzenemethanamine

Intermediate 35

(a) 2-(4-Aminophenoxy)-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylacetamide

A solution of Intermediate 34(a) (37.5g) in ethanol (350 ml) was hydrogenated at room temperature in the presence of 10% palladium on carbon (3.5). After hydrogen absorption was completed, the catalyst was filtered off and the solution

was concentrated to give the title compound (34 g) as an oil. IR includes peaks at 1650cm^{-1} (CO) and 3340-3400cm^{-1} (NH_2).

The following compounds were prepared in a similar manner to Intermediate 35(a).

(b) 2-(4-Aminophenoxy)-N-[(3,4-dimethoxyphenyl)methyl]-N-methylacetamide as an oil. IR includes peaks at 1650cm^{-1} (CO) and 3340-3400cm^{-1} (NH_2).

From Intermediate 34(b).

(c) 2-(4-Aminophenoxy)-N-methyl-N-(phenylmethyl)acetamide as an oil. IR includes peaks at 1660cm^{-1} (CO) and 3300-3420cm^{-1} (NH_2).

From Intermediate 34(c).

(d) 2-(4-Aminophenylthio)-N-[(3,4-dimethoxyphenyl)methyl]-N-methylacetamide as an oil. IR includes peaks at 1645 cm^{-1} (CO) and 3350cm^{-1} (NH_2).

From Intermediate 34(d).

(e) 2-(4-Aminophenoxy)-N-[2-(4-methoxyphenyl)ethyl]-N-methylacetamide as an oil. IR includes peaks at 1630cm^{-1} (CO) and 3350-3420cm^{-1} (NH_2).

From Intermediate 34(e).

(f) 2-(4-Aminophenoxy)-N-[(4-methoxyphenyl)methyl]-N-methylacetamide as an oil. IR includes peaks at 1650cm^{-1} (CO) and 3340-3430cm^{-1} (NH_2).

From Intermediate 34(f).

(g) 2-(4-Aminophenoxy)-N-methyl-N-[(4-methylphenyl)methyl]acetamide as an oil. IR includes peaks at 1650cm^{-1} (CO) and 3350-3420cm^{-1} (NH_2).

From Intermediate 34(g).

(h) 2-(4-Aminophenoxy)-N-methyl-N-[[4-(methylthio)phenyl]methyl acetamide as an oil. IR includes peaks at 1660cm^{-1} (CO) and 3340-3420cm^{-1} (NH

From Intermediate 34(h).

(i) 2-(4-Aminophenoxy)-N-ethyl-N-(phenylmethyl)acetamide as oil. IR includes peaks at 1650cm^{-1} (CO) and 3350-3430cm^{-1} (NH_2).

From Intermediate 34(i).

Intermediate 36

(a) N-[2-(4-Aminophenoxy)ethyl]-3,4-dimethoxy-N-methylbenzeneethanamine

A solution of Intermediate 35(a) (20 g) in THF (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride in THF (100 ml) at room temperature and the mixture was heated under reflux for 3h. Water was added carefully to the cooled mixture which was then filtered, washed with THF, evaporated and extracted with ether. The combined ethereal extracts were dried and evaporated to give the title compound (11 g) as an oil. IR includes a peak at 3350-3430cm-1 (NH_2).

The following compounds were prepared in a similar manner to Intermediate 36(a):

(b) N-[2-(4-Aminophenoxy)ethyl]-3,4-dimethoxy-N-methylbenzenemethanamine as an oil. IR includes a peak at 3360-3420cm^{-1} (NH_2).

From Intermediate 35(b).

(c) N-[2-(4-Aminophenoxy)ethyl]-N-methylbenzenemethanamine as oil. IR includes a peak at 3330-3420cm^{-1} (NH_2).

From Intermediate 35(c).

(d) N-[2-(4-Aminophenylthio)ethyl]-3,4-dimethoxy-N-methylbenzenemethanamine as an oil. NMR includes signals at 2.30 (3H,s,N-CH_3) and 3.85 (6H,s,OCH_3).

From Intermediate 35(d).

(e) N-[2-(4-Aminophenoxy)ethyl]-4-methoxy-N-methylbenzenemethanamine as an oil. IR includes a peak at 3340-3430cm^{-1} (NH_2).

From Intermediate 35(e).

(f) N-[2-(4-Aminophenoxy)ethyl]-4-methoxy-N-methylbenzenemethanamine as an oil. IR includes a peak at 3350-3430cm^{-1} (NH_2).

From Intermediate 35(f).

(g) N-[2-(4-Aminophenoxy)ethyl]-4-methyl-N-methylbenzenemethanamine as an oil. IR includes a peak at 3350-3430cm^{-1} (NH_2).

From Intermediate 35(g).

(h) N-[2-(4-Aminophenoxy)ethyl]-N-methyl-4-(methylthio) benzenemethanamine as an oil. IR includes a peak at 3350-3420cm^{-1} (NH_2).

From Intermediate 35(h).

(i) N-[2-(4-Aminophenoxy)ethyl]-N-ethylbenzenemethanamine as an oil. IR includes a peak at 3360-3430cm^{-1} (NH_2).

From Intermediate 35(i).

Intermediate 37

(a) 3,4-Dimethoxy-N-methyl-N-[3-(4-nitrophenoxy)propyl] benzeneethanamine

A mixture of 1-(3-bromopropoxy)-4-nitrobenzene (18.7 g) and Intermediate 20(a) (14.1g) were heated for 30 min at 140^0 and then diluted with water. The mixture was extracted with dichloromethane, and the organic phase washed with water, dried and concentrated. The residue was purified by column

chromatography eluting with dichloromethane/methanol (95:5) to gi[illegible] title compound (18g) as an oil. NMR includes a signal at d 2.38 (3H,s,N-CH_3).

The following compounds were prepared in a similar manner to In[illegible]ediate 37(a):

(b) 4-Methoxy-N-methyl-N-[3-[illegible]-nitrophenoxy)propyl] benzeneethan[illegible] as an oil. NMR includes a signal at d 2.40 (3H,s,N-CH_3).

From 1-(3-bromopropoxy)-4-nitrobenzene and Intermediate 20(e).

(c) 3,4-Dimethox[illegible]-N-methyl-N-[3-(4-nitrophenoxy)propyl] benzenem[illegible]mine as an oil. NMR includes a signal at d 2.40 (3H,s,N-CH_3).

From 1-(3-bromopropoxy)-4-nitrobenzene and Intermediate 20(b).

(d) 3,4-Dimethoxy-N-methyl-N-[3-[(4-nitrophenyl)thio[illegible]propyl] benzenemethanam[illegible] as an oil. NMR includes a signal at d 2.40 (3H,s,N-[illegible]).

From 1-[(3-bromopropyl)th[illegible]-4-nitrobenzene and Intermediate 20([illegible])

Intermediate 38

(a) N-[3-(4-Aminophenoxy)propyl]-3,4-dimethoxy-N-methylbenzeneeth[illegible]ne

A solution of Intermediate 37(a) (18g) in ethanol (200 ml) was hyd[illegible]nated at room temperature in the presence of 10% palladium on carbon (1 g). After hydrogen absorption was completed, the catalyst was filtered off and th[illegible]lution was concentrated to give the title compound (15g) as an oil. IR include[illegible]ak at 3300-3370cm-1 (NH_2).

The following compounds were prepared in a similar manner to In[illegible]ediate 38(a):

(b) N-[3-(4-Aminophenoxy)prop[illegible]-4-methoxy-N-methylbenzeneethan[illegible] as an oil. IR includes a peak at 3350-3430cm^{-1} (NH_2).

From Intermediate 37(b).

(c) N-[3-(4-Aminophenoxy)propyl]-3,4-dimethoxy-N-methylbenzenemet nine as an oil. IR includes a peak at 3360-3430cm^{-1} (NH_2).

From Intermediate 37(c).

(d) N-[3-[(4-Aminophenyl)thio]propyl]-3,4-dimetho -N-methylbenzenemethanamine as an oil. IR includes a peak at 3370-3450cm H_2).

From Intermediate 37(d).

Intermediate 39

9,10-Dihydro-2-(methylthio)-9-oxo-4-acridinecarboxylic acid

(i) 2-[(2-Carboxyphenyl)amino]-5-(methylthio)benzoic acid

A mixture of 2-chloro-5-(methylthio)benzoic acid (10 g), anthrani d (7 g), potassium carbonate (14 g) and copper (1 g) in 2-(2-methoxyethoxy) anol (100 ml) was heated at 180^0 for 24h. Water (400 ml) was then added. the catalyst was filtered off. The filtrate was acidified with dilute hydrochl cid. The resulting precipitate was filtered off, washed with water, dried, and cr ised from methanol to give the title compound (4.5g) as crystals. IR include ks at 3300cm-1 (NH) and 1700cm-1 (CO_2H).

(ii) 9,10-Dihydro-2-(methylthio)-9-oxo-4-acridinecarboxylic acid

The product of part (i) above (2g) in phosphorus oxychloride (was heated at reflux for 1h. The solution was then cooled (to 0^0), and water (15 was added slowly. The mixture was then heated at 100^0 for 10 min and then pour onto cracked ice. The resulting precipitate was filtered off, washed with w nd crystallised from methanol to give the title compound (1.6g). IR include s at 1690cm-1 (CO_2H) and 1620cm-1 (CO).

Intermediate 40

N-[4-(3-Bromopropoxy)phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamic

(i) N-[4-(3-Bromopropoxy)phenyl]acetamide

A mixture of N-(4-hydroxyphenyl)acetamide (10 g) and potassiu onate (11 g) in DMF (200 ml) was stirred for 20 min at room temper . 1,3-Dibromopropane (35 ml) was then added and stirring was continued f . The mixture was filtered and the filtrate was concentrated in vacuo. The r e was treated with water and extracted with dichloromethane. The organic p e was washed first with dilute sodium hydroxide, then with water, dried and c trated to give a solid which was triturated with hexane to give the title compou 14g), M.p. 120°.

(ii) 4-(3-Bromopropoxy)benzenamine

A mixture of the product of part (i) above (13g) and 5N hydroc acid (200 ml) was heated under reflux for 2 h. After cooling, the mixture w ified with sodium hydroxide solution and extracted with dichloromethane. ganic phase was evaporated to give the title compound (7g) as an oil. IR incl peak at 3360-3450cm-1 (NH).

(iii) N-[4-(3-Bromopropoxy)phenyl]-9,10-dihydro-9-oxo-4-acridinecarbo e

A mixture of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1. nd 1-hydroxybenzotriazole (1.1 g) in DMF (50 ml) was stirred at room temper or 10 min. The product of part (ii) above (1.5g) was then added fo d by dicyclohexylcarbodiimide (1.3 g) and the mixture was stirred at room t ture for 16 h and then filtered. The filtrate was concentrated in vacuo, treate water and extracted with dichloromethane. The combined, dried organic ex were concentrated to give the title compound (0.5g) which was recrystal from acetonitrile, MP 12 .

Intermediate 41

N-[(3,4-Dimethoxyphenyl)methyl]-N-me -4-nitrophenylaminocarbonylmethanamine

A mixture of Intermediate 20(b) (2.8g), Intermediate 56 (3g) and sium carbonate (2.3g) in DMF (50ml) was heated at 60° for 24h. The next then

evaporated, extracted with dichloromethane, washed with water, a and concentrated to give a solid which was recrystallised from diethyl ether ide the title compound (3.7g). MP : 120°.

Intermediate 42

N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl 4-aminophenylaminocarbonylmethanamine

A solution of Intermediate 41 (3.6g) in ethanol (100ml) was hydro d at room temperature in the presence of 10% palladium on carbon (500m ; fter hydrogen absorption was completed the catalyst was removed by filtrat the filtrate was concentrated to give the title compound (3.5g).

NMR includes signals at d 2.5 (3H s,N-CH_3); 3.8 (6H,s,OCH_3).

Intermediate 43

N-[2-(4-Aminophenylamino)ethyl]-3,4-dimethoxy-N-methylbenzenemet e

A solution of Intermediate 42 (3.5g) in THF (50ml) was added dr o a stirred suspension of lithium alum ium hydride in THF (30ml) at room t ure and the mixture was heated under reflux for 48h. Water was added care the cooled mixture which was then filtered on a celite pad. The filtrate was ted to dryness and upon column chromatography (dichloromethane-met the remaining residue gave the title compound (1.4g).

NMR includes signals at d 2.15 (3H,s,N-CH_3); 2.5 and 3 (4H,2t,-CH_2- 3.7 (6H,s,OCH_3).

Intermediate 44

9,10-Dihydro-5,7-dimethoxy-9-oxo-4-acridinecarboxylic acid

A mixture of 2-iodoisophthalic acid (5.8g), 2,4-dimethoxy-aniline and cuprous chloride (1g) in 2,3-butanediol (20ml) and toluene (10ml) w to 120°. After most of toluene has distilled off, N-ethylmorpholine (10ml) ed and the mixture was stirred at 120° for one hour. After cooling and dilut 2N

potassium carbonate the solution was filtered on celite. The filtrate w[illegible]ified with 2N hydrochloric acid and the greenish precipitate was recovered b[illegible]n.

The product (4g) was heated in polyphosphoric acid (50g) at 120[illegible]hour to give the title compound which was recovered as a solid (1.5g) by [illegible]ation with water and purified by dissolving in 1N sodium hydroxide and re[illegible]ation with acetic acid (pH 4).

Analysis Found : C,62.1; [illegible].4.3;

$C_{16}H_{13}NO_5$, 0.5 H_2O Requires : C,62.3; H,[illegible].5%.

The following acid was prepared in a similar manner to Intermedi[illegible]

Intermediate 45

9,10-Dihydro-6,7,8-trimethoxy-9-oxo-4-acridinecarboxylic acid (1.5g). [illegible]udes a peak at 1620cm^{-1} (CO).

From 3,4,5-trimethoxyaniline (3.8g) and 2-iodoisophthalic acid (5[illegible]

Intermediate 46

3-(2-Bromoethyl)nitrobenzene

Phosphorus tribromide (0.94ml) was added dropwise to a so[illegible]f 3-nitrophenethyl alcohol (5g) in anhydrous diethyl ether (30ml) at 0^0. [illegible]ure was stirred at room temperature for 2 hours and then treated with a[illegible] of potassium carbonate and then water. The organic layer was dried and c[illegible]ted in vacuo to give the title compound as an oil (4.51g).

NMR includes d 3.25 (m,2H,CH_2-Ph) and 3.55 (m,2H,CH_2-Br).

Intermediate 47

(a N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-3-nitrobenzeneethan[illegible]

A mixture of Intermediate 4b (2.2g), Intermediate 20(b) (1.71g) a[illegible]um carbonate (1.58g) in DMF (50ml) was heated at 60^0 for 36 hours. The [illegible]was filtered and the filtrate concentrated in vacuo. The residue was treate[illegible]ter and extracted with methylene chloride. The organic extract was dried, c[illegible]ted

an purified by column chroma ography on silica gel eluting with ne chloride/methanol (99:1) to give the title compound as an oil (1g).

NMR includes d 2.2 (s,3H,N-CH_3) and 3.7 (s,6H,2x0CH_3).

In the same w was prepar d the following compound :

(b) N-[(3,4-Dimethoxyphenyl)methyl]-N-methyl-3-(3-nitr y) propanamine

From 3-(3-bro opropoxy)nitrobenzene and Intermediate 20(b).

NMR includes d 2.2 (s,3H,N-CH_3) 3.35 (s,2H,N-CH_2-Ph) and 3.8 (s,6H).

Intermediate 48

(a) 3-Amino-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzeneetha

A solution of Intermediate 47(a) (1g) in ethanol (50ml) was hydr at room temperature in presence of 10% palladium-on-carbon (0.15g) he hydrogen absorptio was complet d, the catalyst was filtered off and on concentrated to give the title compound as an oil (0.8g).

NMR includes d 2.2 (s,3H,N-CH), 3.4 (s,2H,NH_2) and 3.8 (s,6H,2x0(

In the same way was prepared the following compound :

(b) N-[3-(3-Aminophenoxy)propyl]-3,4-dimet N- m ylbenzenemethanamine

From Intermediate 47(b).

NMR includes d 2.2 (s,3H,N-CH_3), 2.7 (s,2H,NH_2), 3.4 (s,2H,N-CH_2- 3.7 (s 6H,2x0CH_3).

Intermediate 49

N-[(3,4-Dimethoxyphenyl)methyl] N-methyl-3-(3-nitrophenyl)-2-propen

A mixture of 3-nitrocinnamic acid (10g) and 1-hydroxybenzotria g) in DMF (100ml) was stirred at room temperature for 10 minutes. Intermi b) (9.2g) was added followed by dicyclohexylcarbodiimide (10.63g). The was

stirred at room temperature for 16 hours and then filtered. The was concentrated in vacuo, treated with dilute hydrochloric acid solution, dilute sodium hydroxide solution and extracted with methylene chloride. anic extract was dried and concentrated to give the title compound (15.63g) NMR includes d 2.7 (s,2H,N-CH_3) and 3.75 (s,6H,2x0CH_3).

Intermediate 50

3-Amino-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzenepropana

A solution of Intermediate 49 (10g) in ethanol (100ml) was hy ed at room temperature in the presence of 10% palladium-on-carbon (1g r the hydrogen absorption was completed, the catalyst was filtered off a rate concentrated in vacuo. The residue was purified by column chroma y on silica gel eluting with methylene chloride/methanol (98:2) to title compound as an oil (5.56g).

NMR d 2.7 (s,2H, N-CH_3) and 3.85 (s,6H,2x0CH_3).

Intermediate 51

3-Amino-N-[(3,4-dimethoxyphenyl)methyl]-N-methylbenzenepropana

A solution of Intermediate 50 (5g) in THF (100ml) was added to a stirred suspension of lithium aluminium hydride (2.31g) in THF (om temperature and the mixture was heated under reflux for 2 hours. Wat was carefully added to the cooled mixture which was then filtered. Th was concentrated, treated with water and extracted with diethyl ether. anic extract was dried, evaporated and the product purified by column chr iphy on silica gel eluting with methylene chloride/methanol (97:3) to title compound as an oil (2.46g).

NMR includes d 2.1 (s,3H,N-CH_3), 3.35 (s,2H,N-CH_2-Ph) and 3.7 (s,6H,2x0CH_3).

Intermediate 52

4-(3-Methoxy-4-nitrophenyl)-3-buten-1-ol

The Wittig reaction in THF (100ml) between 3-methoxy-4-nitrob de
(1 (g) and 3-hydroxypropyltriphenylphosphonium bromide (2) (5.3g ce
of a solution of n-butyllithium (1.6M) in hexane (16.5ml) gave the tit. nd
(2 g) as an oil.

NMR includes sign at (3.4(2H,t,CH_2OH); 3.6(3H,s,OCH_3).

(1) CA 13 (171567 w

(2) A.R. Hands and A.J.H. Mercer, J. Chem. Soc. (c), (1968) 244

Intermediate 53

4 (3-Bromo-1-butenyl)-2-methoxy-1-nitrobenzene

Phosphorus tribromide (0.33ml) was added dropwise to a of
Intermediate 52 (2.6g) in anhydrous diethyl ether (10ml) at 0^0. The as
stirred at room temperature for 1 hour, then washed with a solution (m
carbonate (1M) and with water. The organic layer was dried and con in
evaporated to give the title compound (3.3g) as a yellow oil. NMR includes d
3.6(2H,t,CH_2-Br); 3.8(3H,s,O-CH_3).

Intermediate 54

N-[4-(3-Methoxy-4-nitrophenyl)-3-butenyl]-3,4-dim N-
methylbenzenemethanamine

A mixture of Intermediate 53 (3.3g), Intermediate 20(b) (2.5g) a m
carbonate (1.9g) in DMF (20ml) was stirred at room temperature f he
mixture was filtered and the filtrate was evaporated. The residue w nto
water and extracted with dichloromethane. The organic layer was ith
washed, dried, filtered and evaporated. The oily residue was then purifie gel
column chromatography eluting with dichloromethane/ methanol (95: he
The title compound (3g) as an oil. NMR includes signals at d 2.1(3H);
3.6(6H,s,2xOCH_3); 3.8(3H,s,OCH_3).

Intermediate 55

5 p[illegible]-amino-N-[(3,4-dimethoxyphenyl)methyl]-3-me[illegible]-N-m[illegible]ylbenzenebutanamine

A solution of Intermediate 54 (1.2g) in a mixture of ethanol (50m[illegible] ar[illegible]yl a[illegible]te (20ml) was hydrogenated at room temperature in the prese[illegible]% p[illegible]dium-on-carb[illegible] (0.1g). After the hydrogen absorption was co[illegible]e .he catalyst was filtered off and the solution concentrated to give the titl[illegible] nd (1g) as an oil. NMR includes signals at d 2.1 (3H,s,N-CH_3); 3.65(3H[illegible],O [illegible]); 3.7(6H,s,2xOCH_3).

10 Intermediate 56

2-Chloro-N-(4-nitrophenyl)acetamide

Chloroacetyl chloride (11ml) was added dropwise to a stirred [illegible]ix of potassium carbonate (18.8g) and 4-nitroaniline (15g) in DMF (100ml) m[illegible]t at 0°C. The mixture was then allowed to stand overnight at room temp[illegible] nd 15 p[illegible] into cr[illegible]she[illegible]e. A yellow solid was recovered and crystallised [illegible]-ne containing isoprop[illegible] alcohol (10[illegible]) to give the title compound (10g), MP [illegible]0. NMR includes signals at d 4.1(2H,s,$COCH_2Cl$); 7.4-8.1(4H,m,a[illegible]m[illegible]s); 10.3(1H,bs,NH).

20 Intermediate 57

3,4-Dihydro-6,7-dimethoxy-N-(4-nitrophenyl)-2(1H)-isoquinolineacetan[illegible]e

A mixture of intermediate 56 (10.3g), potassium carbonate (8g) [illegible],4-tetrahydro-6,7-dimethoxyisoquinoline (9.3g) in DMF (100ml) was heate[illegible]ht at 60°. After cooling, the reaction mixture was poured onto ice and t[illegible]ole 25 material recovered and dried to give the title compound, MP : 173-[illegible]8°C IR in[illegible]des signals at [illegible].8(4H,s,2xCH_2), 3.2(2H,s,$COCH_2$-N); 3.7(2H,s,[illegible]); 3.[illegible](6H,m,2xOCH_3); [illegible]-8.15(6H,[illegible]aromatics); 9.3(1H,bs,NHCO).

Intermediate 58

30 N-(4-Aminophenyl)-3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolineaceta[illegible]id

A suspension of Intermediate 57 (15g) and 10% palladium-on-car n in etnanol (200ml) was stirred at room temperature under a slight over s of hydrogen. After 2h the catalyst was filtered off, and wa ed h dichloromethane/methanol (9:1). The filtrate and washing were concentra d ie crystalline residue gave upon washing with ethanol and drying the title on id (10.6g), MP : 185°. NMR includes signals at d 2.8(4H,s,2xCH_2); 3.15 H)- CH_2-N); 3.6(2H,s,Ph-CH_2-N); 3.7(6H,s,2xOCH_3); 6.15-7.3(6H,m,a m); 8.63(1H,bs,CONH).

Intermediate 59

N-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]-1,4-benze d e

A solution of borane in tetrahydrofuran (1M; 35.4ml) was added a d so'ution of Intermediate 58 (2g) in THF (150ml). After 4h of refluxing t r n mixture was cooled, treated with concentrated hydrochloric acid to na ie solution up to 3N in hydrochloric acid and then refluxed again for 1: ni N Sodium hydroxide was added and the mixture was extracted with dichlo m e. The organic layer was washed with water, dried and concentrated to giv a r ie which after purification by silica gel column chromatography el tin th toluene/isopropylamine (95:5) gave the title compound as an oil (1 g). R includes signals at d 2.6(4H,bs,Ph-CH_2-CH_2-N); 3.45(4H,s,CH_2- H d PhCH_2-N); 3.6(6H,s,2xOCH_3); 6.3(6H,s,aromatics).

Intermediate 60

4-[2-(2,3-Dihydro-5,6-dimethoxy-1H-isoindol-2-yl)ethyl]benzenamine

4,5-Bischloromethyl veratrol (2.35g; S. H. Wood, M. A. Peny and C g, J. A. C. S., (1950), 72, 2989-2991) was added at room temperature a d suspension of 50% aqueous sodium hydroxide (5ml), toluene (.5r 4- aminophenylethylamine (1.5g) and Aliquat (0.2g). The heterogeneous r xtu as stirred at room temperature for 16 hours, poured in water and extr te h methylene chloride. The organic layer was dried and the solvent ev or in vacuo. The residue was purified by column chromatography on silica el g

with methylene dichloride/methanol (95:5) to give the title compo: id . solid (0.6g), MP : 150^0. NMR includes signals at d 2.7(4H,m,Ph-C 2- -N); 4.6(2H,bs,NH2); 3.7(6H,s,2xOCH$_3$); 3.8(4H,s,2xN-CI P 5.2- (6H,m,aromatics).

Intermediate 61

1-(4-Nitrophenyl)-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinol: yl) one hydrobromide

A solution of 6,7-dimetho:y-1,2,3,4-tetrahydroisoquinoline (1: 63 d 2-bromo-4'-nitroacetophenone (16.47g) in a mixture of ethanol 5(and methylene chloride (150ml) was heated at 60^0 for 24 hours. After co: ing om temperature yellow crystals appeared. These were collected by filtrat n : ried in vacuo to give the title compound (9.4g); MP : 216^0. NMR(D$_6$-DM O) ides signals at d 3.6(6H,s,2xOCH$_3$); 4.2(2H,s,N-CH$_2$-Ph); 4.95(2H,s,( )-(-N); 6.6(2H,aromatics isoquinoline); 8(4H,m,aromatics).

Intermediate 62

3,4-Dihydro-6,7-dimethoxy-a-(4-nitrophenyl)-2(1H)-isoquinolineethan

To a suspension of Intermediate 61 (9.4g) in methanol (600m wa ded portionwise sodium borohydride (2.44g) and the mixture was stir d om temperature for 16 hours. The reaction was diluted with water (200ml) filt and evaporated in vacuo. The residue was extracted with methylene chloride and hed with water. The organic layer was dried and evaporated in vacuo to ; ve itle compound (1.15g), after crystallisation from ethanol, MP : 130^0. NMR i des signals at d 2.4-3.1(6H,m,3xCH$_2$); 3.7(6H,s,2xOCH$_3$); 4.2(1 1,H -H); 4.8(1H,m,H-C-OH); 6.1-8.1(6H,m,aromatics).

Intermediate 63

a-(4-Aminophenyl)-3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinectha l

A solution of intermediate 62 (2.4g) in ethanol (200ml) was hyd ge at room temperature in the presence of 10% palladium-on-carbon ((3g ter

hydrogen absorption was completed, the catalyst was filtered off and the solvent was concentrated to give the title compound (1.9g) as a white solid, mp: 90°. NMR includes signals at δ 2.4-2.9(6H,m,3xCH$_2$); 3.5(2H,s,CH$_2$); 3.8(6H,s,2xOCH$_3$); 4.55(2H,s,PhCH$_2$OH); 6.25-7.1(6H,m,aromatics).

Intermediate 64

2-Bromo-N-methyl-N-[(4-nitrophenyl)methyl]acetamide

To a solution of bromoacetyl bromide (30g) in methylene chloride (200ml) at 0° was added a solution of N-methyl-4-nitrobenzenemethanamine (13.3g, I. Watson, J. Chem. Soc., 1926, 2461) in methylene chloride (100ml) and triethylamine (12ml). The reaction was stirred 5 min. at 0° and then water (200ml) was added. The methylene chloride layer was dried and evaporated in vacuo. The residue was purified by column chromatography eluting with methylene chloride:methanol (95:5) to give the title compound (25g) as an oil. NMR includes signals at δ 3.1(3H,s,N-CH$_3$); 3.9(2H,s,CH$_2$Br); 4.55(2H,s,Ph-CH$_2$-N); 8.2(4H,m,aromatics).

Intermediate 65

3,4-Dihydro-6,7-dimethoxy-N-methyl-N-[(4-nitrophenyl)methyl]-1-isoquinolineacetamide

A mixture of Intermediate 64 (1.8g), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.4g) and potassium carbonate (1.6g) in DMF (100ml) was stirred overnight. After removal of insoluble material by filtration the solvent was evaporated in vacuo and the residue partitioned between dichloromethane and water. The organic phase was dried, then concentrated under reduced pressure to give the product, after purification by column chromatography eluting with methylene chloride/methanol (95:4), gave the title compound (1.65g). NMR includes signals at δ 2.6(4H,m,2xCH$_2$); 3.0(3H,s,N-CH$_3$); 3.33(2H,s,CO-CH$_2$-Ar); 3.6(2H,s,Ph-CH$_2$-N); 3.7(6H,s,2xOCH$_3$); 4.55(2H,s,Ph-CH$_2$-NHCO); 6.2-8.2(6H,m,aromatics).

Intermediate 66

N-[(4-Aminophenyl)methyl]-3,4-dihydro-6,7-dimethoxy-N-methyl-2(1H)-isoquinolineacetamide

A solution of Intermediate 65 (1.65g) in ethyl acetate (100ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-carbon (0.34g). After hydrogen absorption was complete the catalyst was filtered off and the solution was concentrated to give the title compound (1.3g) as a white solid, MP : 175-215°. NMR includes signals at d 2.8(7H,s,N-CH3 and 2xCH2); 3.2(2H,s,CO-CH2-N); 3.5(2H,s,N-CH2-Ph); 3.7(6H,s,2xCH3

Intermediate 67

N-[(4-Aminophenyl)methyl]-3,4-dihydro-6,7-dimethoxy-N-methyl-2(1H)-isoquinolineethanamine

A solution of Intermediate 66 (1.49g) in THF (150ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.47g) in THF (100ml) from room temperature for 4 hours. Water (5ml) was added carefully to the cooled mixture which was filtered and the filtrate concentrated and the residue extracted with methylene chloride. The organic layer was dried and evaporated. The resulting product was purified by column chromatography on silica gel eluting with methylene chloride/isopropylamine (92:8) to give the title compound as an oil (0.7g). NMR includes signals at d 2.15(3H,s,N-CH3); 2.55(8H,m,CH2); 3.35(2H,s,NH2); 3.65(6H,s,2xOCH3); 6.3-7.1(6H,m,aromatics)

Intermediate 68

2-[[(3,4-Dimethoxyphenyl)methyl][methylamino]-2-methylpropyl]-4-nitrophenyl)methyl]acetamide

A mixture of Intermediate 64 (4.3g), Intermediate 20(b) (3.26g) and potassium carbonate (4.14g) in DMF (100ml) was stirred overnight. The mixture was filtered, and the filtrate concentrated in vacuo to a residue which was extracted with methylene chloride. After washing with water and drying, the organic layer was evaporated to a syrup which was purified by column chromatography on silica gel eluting with ethyl acetate/cyclohexane (1:1) to give the title compound as an oil

(5.7g). NMR includes signals at δ 2.3(3H,s,N-CH_3); 3.7(6H,s, xC); 4. H,s,Ph-CH_2-NHCO).

Intermediate 69

N-(4-Aminophenyl)methyl-2-[(3,4-dimethoxyphenyl)methyl -meth im N-methylacetamide

A solution of Intermediate 68 (5.7g) in a mixture of ethyl acetat ol (1:2) (100ml) was hydrogenated at room temperature and atmospheric re in the presence of 10% palladium-on-carbon (0.8g). After hydrogen abs pti as completed, the catalyst was filtered off and the filtrate was concentrate o ne title compound (5.2g) as an oil. NMR includes signals at δ 3.8(6H, x( ); 4.5(2H,s,Ph-CH_2-NCO).

Intermediate 70

N-[(4-Aminophenyl)methyl]-N'-(3,4-dimethoxyphenyl)methyl]-N,N di l-1,2-ethanediamine

A solution of Intermediate 69 (5.2g) in THF (150ml) was added o at room temperature to a stirred suspension of lithium aluminium hydride g) iF (5 ml). After 4 hours, water (10ml) was added carefully to the co d re which was then filtered. The filtrate was concentrated to dryness and ne ue diluted with methylene chloride and extracted with hydrochloric aci (1N ne aqueous layer was basified with an aqueous solution of sodium hydroxi (nd extracted with methylene chloride. The organic layer was dri a n concentrated in vacuo. The residue was purified by column chrom gr on silica gel eluting with cyclohexane/methylene chloride/isopropylam (to give the title compound as an oil (2g). NMR includes si a d 2. (6H,s,2xNCH_3); 2.4(4H,s,2xNCH_2); 3.2(4H,m,2xN- H); 3. 6H,s,2xOCH_3); 3.85(2H,s,NH2); 6.1-7.5(7H,m,aromatics)

Intermediate 71

3,4-Dimethoxy-N-methyl-N-[4-(4-nitrophenyl)-2-butenyl] benzenemeth am

A mixture of Intermediate 20(b) (9g), potassium carbonate (5g) ro-
nitrophenyl)-2-butene (10.6g, Morgan and al., J. Med. Chem., 8, 98-
5) in 4-methyl-2-pentanone (100ml) was refluxed for 18 hours. ng,
mixture was filtered and evaporated in vacuo. The residue wa by
column chromatography eluting with methylene chloride/methanol (97. 2. ive
title compound (2g) as an oil. NMR includes signals at 2.2(3 3);
6H,s,2xOMe); 5.7(2H,m,double bond); 6.9(3H,m,aromatics PhOM nd
8.15(4H,2d,aromatics $PhNO_2$).

Intermediate 72

N-[3-(4-Aminophenyl)-2-butenyl]-3,4-dimethoxy-N-methylbenzeneme

Intermediate 71 (1.7g) was dissolved at room temperature wit a
ture of methanol (50ml) and concentrated hydrochloric acid (2ml). er
5g) was then added slowly, and the reaction mixture was heated un for
The mixture was then evaporated, basified with sodium hydroxide ed
with diethyl ether. The organic layer was dried and evaporated in vac he
title compound (0.21g) as an oil. NMR includes signals at 2.15(3 s, 3);
3.3(6H,s,2xOMe); 5.55(2H,m,double bond); 6.3-7.2(7H,m,aromatics).

Intermediate 73

3,4-Dimethoxy-N-methyl-N-[3-(4-nitrophenyl)-2-propenyl] benzeneme

A mixture of Intermediate 20(b) (3.6g), 1-chloro-3-(4-nitropheny 2 ne
(3.9g; Cignarella and al., J. Med. Chem., 8, (1965), 326-329) an m
potassium carbonate (3.5g) in 4-methyl-2-pentanone (60ml) was refluxed for 3 er
cooling, the mixture was filtered and the filtrate was evaporated to dr ne
residue was purified by column chromatography eluting with ne
chloride/methanol 95:5) to give the title compound (4.9g) as an oil. NMR es
signals at 2.25(3H,s,NCH_3); 3.2(2H,d,N-CH_2-CH=CH); 3.5(2H);
3.8(6H,s,2xOMe); 6.55(2H,m,double bond); 6.8(3H,d,aromatics);
7.4 and 8.1(4H,2d,aromatics $PhNO_2$).

Intermediate 74

5-[2-[(3,4-Dimethoxyphenylmethyl]methylamino]-1-propenyl] benzen

Intermediate 73 (4.8g) was dissolved in a mixture of methanol concentrated hydrochloric acid (10ml) at room temperature with s powder (5g) was then added slowly and the reaction mixture was reflu After cooling, the mixture was evaporated, diluted with water (20ml), b sodium hydroxide solution, concentrated and extracted with diethyl organic layer was dried and evaporated to give the title compound (3.9 NMR includes signals at d 2.2(3H,s,NCH_3); 3.15(2H,d,N-CH_2 3.6(2H,s,NCH_2Ph); 3.6(2H,s,NH_2), 3.8(6H,s,2xOMe); 5.7-7.6(9H,m,ar double bond).

Intermediate 75

1,2,3,4-Tetrahydro-6-methoxy-2-[2-(4-nitrophenyl)ethyl]isoquinoline

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (6.4g), 1,2,3,4-t methoxyisoquinoline (4.6g; Daniel J. Sall and Gary L. Grunewald, J. 1987, 30, 2208-2216) and potassium carbonate (9.7g) in DMF (150ml) at 50° for 15 h. The mixture was evaporated to dryness and the extracted with dichloromethane. The organic layer was washed dried, filtered and evaporated. The residue was then purified by chromatography eluting with dichloromethane/methanol (98:2) to compound (2g) as an oil which solidified on standing.

NMR includes signals at d 3.6 (2H,m,N-CH_2Ar), 3.7 (3H,s,OCH_3).

Intermediate 76

4-[2-(1,2,3,4-Tetrahydro-6-methoxy-2-isoquinolinyl)ethyl]-benzenamin

A solution of Intermediate 75 (2g) in ethanol (100ml) was hyd room temperature in the presence of 10% palladium-on-carbon (0.2 hydrogen absorption was completed, the catalyst was filtered off and th concentrated in vacuo to give the title compound (1.8g) as an oran solidified on standing.

NMR includes signals at d 3.4 (2H,s,NH_2), 3.55 (2H,s,N-C[illegible] 65
s,OCH[illegible]

[illegible]rmediate 77

1-(3,4-Tetrahydro-6,7-dimethoxy-2-[3-(3-nitrophenyl[illegible]-2-
[illegible]enyl]isoquinoline

A mixture of 3-nitrocinnamic acid (10g) and 1-hydroxybenzotri[illegible]) in
DMF (100ml) was stirred at room temperature for 10 min. 1,2,3,4-[illegible]ro-
[illegible]-dimethoxy-isoquinoline (10g) was then added, fol by
dicyclohexylcarbodiimide (10.6g) and the mixture was stirred at 50° and
then filtered. The filtrate was concentrated in vacuo, treated with di[illegible]um
hydroxide and extracted with dichloromethane. The dried organic was
evaporated and purified by column chromatography eluting with dichlo[illegible]ne/
methanol (9[illegible]) to give the title compound (7.8g). NMR includes a sig .85
s,OCH_3

Intermediate 78

1-[3-(3-Aminophenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-is[illegible]e

A solution of Intermediate 77 (7.8g) in ethanol (100ml) was hydr[illegible]at
atmospheric temperature in the presence of 10% palladium-on-carbon (1g) [illegible]he
hydrogen absorption was completed, the catalyst was filtered off and [illegible]ate
concentrated in vacuo to give the title compound (6.8g).
IR: Freq CO 1640 cm-1, Freq NH_2: 3450 cm-1.

Intermediate 79

1-[3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl] benzena

A solution of Intermediate 78 (6.8g) in THF (100ml) was added d[illegible]o a
stirred suspension of lithium aluminium hydride (3g) in THF (100m[illegible]om
temperature and the mixture was heated under reflux for 3 h. Water w[illegible]led
carefully to the cooled mixture which was filtered, evaporated and ext[illegible]ith

ether. The extract was dried and evaporated to give the title compound (5.4g) as an oil which solidified on standing.

IR: Freq NH_2: 3350-3450 cm-1.

Intermediate 80

1-[(3,4-Dimethoxyphenyl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol

A mixture of 1,2-epoxy-3-(4-nitrophenoxy)propane (6g; Sigma) and Intermediate 20(b) (5g) in isopropanol (100ml) was heated under reflux for 4h and evaporated. The oily residue was crystallised from ether to give the title compound (8.6g) as a white solid.

NMR includes signals at d 2.3 (3H,s,N-CH_3), 3.9 (6H,s,OCH_3).

Intermediate 81

1-(4-Aminophenoxy)-3-[[(3,4-dimethoxyphenyl)methyl]methylamino]-2-propanol

A solution of Intermediate 80 (8g) in ethanol (100ml) was hydrogenated at room temperature in the presence of 10% palladium-on-carbon (0.8g). After the hydrogen absorption was completed, the catalyst was filtered off and the filtrate concentrated in vacuo. The oily product was then purified by column chromatography eluting with dichloromethane/methanol (95:5) to give the title compound (5.8g) as an oil. NMR includes signals at d 2.25 (3H,s,N-CH), 3.8 (6H,s,OCH_3).

Intermediate 82

3,4,5-Trimethoxy-N-methyl-N-[3-(4-nitrophenoxy)propyl]benzenemethanamine

A mixture of 1-(3-chloropropoxy)-4-nitrobenzene (4.6g), 3,4,5-trimethoxy-N-methylbenzenemethanamine (4.1g; Sigma) and potassium carbonate (7g) in DMF (60ml) was heated at 70° for 24 h. The mixture was then filtered and the filtrate evaporated. The residue was taken up in water and extracted with dichloromethane. The organic layer was washed with water, dried, evaporated and purified by column chromatography eluting with dichloromethane/methanol 9:1)

...ive the ... compound (5.8g) ...s a yellow oil. NMR includes signals ... d 2.15 ... s,N-CH_3) ... 2H,s,CH_2-Ar) 3.7 (9H,s,OCH_3).

...mediate ...

N-[3-(4-Aminophenoxy)propyl]-3,4,5-trimethoxy-N-methylbenzenemeth...line

A solu...n of Intermediate ...2 (5.8g) in ethanol (100m.) was hydro...ated at ...om temperature in the presence of 10% palladium-on-carbon (...5 ... After ...drogen absorption was completed, the catalyst was filtered off an...h ...olution ...s concent...ted to give the title compound (5.1g) as an oil. NMR inclu... signals ... 2.25 (3H,...N-CH_3), 3.5 (2H,s,CH_2-Ar), 3.8 (9H,s,OMe)

...mediate ...

...,3,4-Tetrahydro-6,7-dimethoxy-2-[(4-methoxy-3-nitrophenyl)acetyl iso...noline

A mixture of 4-methox...-3-nitrophenylacetic acid (1.2g) ... 1-...hydroxybenzotriazole (0.95g) in DMF (30ml) was stirred at room temp...ture for ...min. 1,2,3,4-Tetrahydro-6,7-dimethoxy-isoquinoline (1.3g) in DM... (... ml) was ...then added, followed by dicyclohexylcarbodiimide (1.2g) and the m... re was ...ed at room temperature for 6 h and then filtered. The filtrate was co...rated in ...vo, treated with dilute sodium hydroxyde and extracted with ethyl ac...te. The ...ed organic extract was evaporated to give the title compound (1.5g) ...s an oil ...which crystallised from ethanol as a white solid, MP 175°. IR: Freq ...: ...50 cm-

...mediate ...

...[3-Amino-4-methoxyphenyl)acetyl]-1,2,3,4-tetra...-6,7-...methoxyisoquinoline

A solu...n of Intermediate 84 (1.6g) in ethanol ...0m.) wa... hy...ated at ...om temperature in the presence of 10% palladium on carbon ... After ...rogen a...rption was comple...ed, the catalyst was ...tered o... ... olution ...s concentrated to give the title compound (1.4g) as an oil. IR: Freq ...50 cm-1 Freq NH_2 3340-3440 cm-1

Intermediate

5-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]-2-methoxybenzenamine

A solution of Intermediate 85 (1.4g) in THF (30ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.9g) in THF (50ml) at room temperature and the mixture was heated under reflux for 3 h. Water was carefully added cautiously to the cooled mixture which was then filtered, evaporated and extracted with ether. The extract was dried and evaporated to give the title compound (1.2g) as an oil which solidified on standing.

IR (Nujol) NH$_2$ 3440, 3340 cm-1.

Intermediate 84

1,2,3,4-Tetrahydro-2-[3-(4-nitrophenoxy)propyl]isoquinoline

A mixture of 1-(3-bromopropoxy)-4-nitrobenzene (10g), 1,2,3,4-tetrahydroisoquinoline (5.1g) and potassium carbonate (10.6g) in DMF (100ml) was stirred at 70° for 24 h. The mixture was then filtered and the filtrate evaporated. The residue was taken up with water and extracted with dichloromethane. The organic layer was washed with water, dried, evaporated and purified by column chromatography eluting with dichloromethane:methanol (98:2) to give the title compound (8.8g) as a yellow oil. NMR included signals at δ 3.7 (2H,s,N-CH$_2$-Ar), 4.1 (2H,t,O-CH$_2$).

Intermediate 85

4-[3-(1,2,3,4-Tetrahydro-2-isoquinolinyl)propoxy]benzenamine

Intermediate 84 (8.8g) was dissolved in a mixture of methanol (100ml) and concentrated hydrochloric acid (50ml) at room temperature with stirring. Iron powder (7.0g) was then added portionwise and the mixture was heated under reflux for 2 h. The mixture was then cooled, poured onto ice, basified with sodium hydroxide and extracted with ethyl acetate. The organic layer was washed

:ater, dried and evaporated to give the title compound (4.5g) as a NMR
: ide: si . 3.7 (2H,s,N CH_2Ar), 3.9 (2H,t,O-CH_2).

: termediate 89

. 2,3,4-Tetrahydro-7-methoxy-2-[2-(4-nitrophenyl)ethyl]isoquinoline

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (3.7g), 1,2,3,4-tetrahydro-7-
:noxyisoquinoline (2.7g; Daniel J. Sall and Gary L. Grunewald, J. Chem.
:, 30, 2205-2216) and potassium carbonate (6.7g) in isopropanol was
:ired under reflux for 48 h. The mixture was evaporated to dryness and the
:sidue was extracted with dichloromethane. The organic layer was washed with
:ter, dried, filtered and evaporated. The residue was then purified by column
: chromatography using dichloromethane/methanol (99:1) to give the title
:mpound (as an orange solid, MP: 92-94°. NMR includes s at 3.6
(2H,m,N-CH_2Ar), 3.7 (3H,s,OCH_3).

: .ermediate 90

: [2-(1,2,3,4-Tetrahydro-7-methoxy-2-isoquinolinyl)ethyl]-benzenamin

A solution of Intermediate 89 (1.6g) in ethanol (150ml) was hydrogenated at
: om temperature in the presence of 10% palladium-on-carbon (0.1 After the
: ydrogen absorption was completed, the catalyst was filtered off and the filtrate was
: concentrated in vacuo to give the title compound (1.4g) as a white s MP: 82-
: 0.

: MR includes signals at 3.4 (2H,s,NH_2), 3.47 (2H,s,N-C , 3.55
: s,OCH_3).

Intermediate 91

: 2,3,4-Tetrahydro-6,7-dimethoxy-2-[2-(3-nitrophenyl)ethyl]isoquino

A mixture of 1-(2-bromoethyl)-3-nitrobenzene (2.3g), 1,2,3,4-tetrahydro-6,7-
: dimethoxyisoquinoline hydrochloride (2.3g) and potassium carbonate MF
: (5ml) was heated at 50° for 12 h. The mixture was then filtered and the filtrate
: evaporated. The residue was then taken up in water, extracted with

dichloromethane, dried, evaporated and purified by column chro: ay
el ing with ...romethane/methanol (99:1) to give the title compo: as
a yellow oil. NMR includes signals at d 3.6 (2H,s,N-CH_2Ar), 3.75 (6H,s

Intermediate 92

3-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl] benzenam

A solution of Intermediate 91 (1.4g) in ethanol (50ml) was hyd at
room temperature in the presence of 10% palladium-on-carbon (0. er
hydrogen absorption was completed, the catalyst was filtered off and the as
concentrated in vacuo to give the title compound (1.15g) as a yello ch
solidified
NMR includes signals at d 3.6 (2H,s,N-CH_2Ar), 3.75 (6H,s,(.5
(2H,s,NH_2).

Intermediate 93

N-[(3,4-Dimethoxyphenyl)methyl]-4-methoxy-N-methyl-3-nitrobenzene e

A mixture of 4-methoxy-3-nitrobenzeneacetic acid (1.2g; CA 67, d
1-hydroxybenzotriazole (0.95g) in DMF (30ml) was stirred for 10 min. te
2(3b) (1.1g) in DMF (20ml) was then added, followed by dicyclohexyl le
(1.1g) and the mixture was stirred at room temperature for 6h and then The
filtrate was concentrated in vacuo, treated with dilute sodium hyd id
extracted with ethyl acetate. The dried, organic extract was evaporated t oil
which was purified by column chromatography elu h
dichloromethane/methanol (95:5) to give the title compound (1.5g) as an
IR: Freq CO 1640 cm-1.

Intermediate 94

3-Amino-N-[(3,4-dimethoxyphenyl)methyl]-4-methoxy- l-
benzeneacetamide

A solution of Intermediate 93 (1.45g) in ethanol (40 ml) was pe at
room temperature in the presence of 10% palladium-on-carbon (0.25, ne

[illegible]rogen absorption was completed, the catalyst was filtered off an[illegible] tion [illegible]s concentrated to give the title compound (1.2g) as an oil.

IR: Freq CO [illegible]1630 cm-1, Freq NH_2 : 3350-3450 cm-1.

Intermediate 95

3-Amino-N-[(3,4-dimethoxyphenyl)methyl]-1-methoxy[illegible]yl-[illegible]propanethiamide

A solution of Intermediate 94 (1.2g) in THF (30ml) was added [illegible] to a stirred suspension of lithium aluminium hydride (0.9g) in THF (2[illegible] om temperature and the mixture was heated under reflux for 3 h. Wa[illegible] ded carefully to the cooled mixture which was then filtered, w[illegible]ash THF, evaporated to dryness and extracted with ether. The extract was dried and evap[illegible] give the title compound (1g) as an oil.

IR: Freq NH_2 : 3350-3450 cm-1.

Intermediate 96

1,2,3,4-Tetrahydro-5,6-dimethoxy-2-[2-(4-nitrophenyl)ethyl] isoquinoline

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (0.3g), 1,2,3,4-tetrahydro-5,6-dimethoxyisoquinoline (0.25g; R. D. Haworth, J. Chem. Soc., 1947); Robin D. Clark, J. Med. Chem., 596-600, 33, (1990)) and potassium carbonate (0.5g) in DMF (25ml) was heated at 60^0 for 3 h. The mixture was then cooled and the filtrate evaporated. The residue was taken up in water, extracted with dichloromethane, dried, evaporated and purified by column chromatography using dichloromethane/methanol (99:1) to give the title compound as an orange solid, MP 97^0. NMR includes signals at δ 3.75 (3H,s,OCH_3),

Intermediate 97

4-[2-(1,2,3,4-Tetrahydro-5,6-dimethoxy-2-isoquinolinyl)ethyl]-benzen[illegible]

A solution of Intermediate 96 (0.3g) in ethanol (2[illegible]ml) was hy[illegible]at room temperature in the presence of 10% palladium-on-carbon (0[illegible]the

...drogen absorption was completed, the catalyst was filtered off and t... ...as concentrated in vacuo to give the title compound (0.22g) as a yello... ...IR includes signals at 3.55 (2H,s,N-CH_2Ar), 3.65-3.85 (8H, OCH_3 and ...

Intermediate 98

...,3,4-Tetrahydro-6,7,8-trimethoxy-2-[2-(4-nitrophenyl)ethyl] isoquin...

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (0.... g), 1,2,3-tri-methoxy-6,7,8-trimethoxyisoquinoline [0.33g; J. Chem. Soc. D, (2..), 1296-1297] and potassium carbonate (0.5g) in DMF (20ml) was heated at 50° for 12 h... ...was then filtered and the filtrate evaporated. The residue was taken... ...extracted with dichloromethane, dried, evaporated and purified ... ...chromatography eluting with dichloromethane/methanol (99:1) to ... ...compound (0.34g) as a red solid, MP:110°. NMR includes signals at ... (2H,s,N-CH-Ar), 3.70 (6H,s,OCH_3), 3.75 (3H,s,OCH_3).

Intermediate 99

...[2-(1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-isoquinolinyl)ethyl]-benz...

A solution of Intermediate 98 (0.34g) in ethanol (10ml) was hy... at room temperature in the presence of 10% palladium-on-carbon (0.0... Af... the hydrogen absorption was completed, the catalyst was filtered off a... ...was concentrated in vacuo to give the title compound (0.3g) as a whi... ...solid ...°. NMR includes signals at d 3.55 (2H,s,N-CH_2Ar), 3.7-3.7... (11H, OCH_3 ...).

Intermediate 100

...3,4-Tetrahydro-6,7-dimethoxy-2-[2-(4-nitrophenyl)ethyl] isoquino...

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (9.0... g), 1,2,3,4-t... ...6,7-dimethoxyisoquinoline hydrochloride (10.59g) and potassium carbon... ...in isopropanol (150ml) was refluxed for 48h. The mixture was then f... ...the filtrate evaporated to dryness. The resulting residue was taken u... ...and extracted with dichloromethane. The organic layer was washed wi... ...ed

and evaporated to give an oil which crystallised in a mixture of 2-[illegible] nd diethyl ether to give the title compound (10.27g). M.p. : [illegible] 119^0.

Analysis Found : C,66.48; H,6.48; [illegible] 14;

$C_{19}H_{22}N_2O_2$ requires : C,66.65; H,6.48; [illegible] 18%.

Intermediate 101

4-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]benzen[illegible]

Method a :

A solution of Intermediate 100 (20g) in ethanol (30[illegible]) was hy[illegible] at room temperature and atmospheric pressure in the presence of 10 % p[illegible] n-carbon (2g). After the hydrogen absorption was complete[illegible] the catalyst [illegible]ed off and the filtrate was concentrated to give the title compound (17[illegible] as oil which solidified by scratching in hexane.

Method b :

Iron powder (12.44g) was added portionwise at room temperature [illegible]ed to a solution of Intermediate 100 (14g) in a mixture of methanol [illegible]nd concentrated hydrochloric acid (150ml). After heating under reflux f[illegible] the mixture was cooled, poured onto ice, basified with a solution of sodi[illegible]de and extracted with ethyl acetate. The organic layer was washed with [illegible]ed and evaporated to give the title compound. M.p. : 128^0 (ethanol).

Analysis Found : C,72.77; H,7.80; [illegible]7;

$C_{19}H_{24}N_2O_2$ requires : C,73.05; H,7.74; [illegible]97%.

Example 1

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetra[illegible]o-6,7-d[illegible] 2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

A mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acri[illegible] carboxy[illegible] g) and 1-hydroxybenzotriazole (0.43g) in DMF (30ml) was stirred at [illegible]e for 10min. Intermediate 2(c) (1g) in DMF (20ml) was then added, w[illegible]y dicyclohexylcarbodiimide (0.66g) and the mixture was stirred at room te[illegible]re

for 16h and then filtered. The filtrate was concentrated in vacuo, treated with sodium hydroxide solution and extracted with dichloromethane. The organic layer was then washed with water, dried and evaporated to give a residue which was purified by column chromatography eluting with dichloromethane:methanol (95:5) to give a solid which was recrystallised from isopropanol and filtered off to give the title compound (0.4g), m.p. 215-225°.

Analysis Found : C,72.3; H,5.9; N,7.[illegible]%

$C_{41}H_{33}N_3O_4$ requires : C,72.5; H,5.9; N,7.39%.

Example 2

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thiophenyl]-4-acridinecarboxamide

A mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.[illegible]g) and 1-hydroxybenzotriazole (0.35g) in DMF (20ml) was stirred at room temperature for 10min. Intermediate 2(b) (0.9g) in DMF (20ml) was then added, followed by dicyclohexylcarbodiimide (0.5g) and the mixture was stirred at room temperature for 1h and then filtered. The filtrate was concentrated in vacuo, treated with sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated to leave an oil which was purified by column chromatography eluting with dichloromethane:methanol (97:3). The resulting solid was recrystallised from acetonitrile and filtered off to give the title compound ([illegible]), m.p. [illegible]°

Analysis Found : C,67.7; H,5.9; N,[illegible]; S,3.5.2;

$C_{45}H_{35}N_3O_4S(0.5H_2O)$ requires : C,67.9; H,5.9; N,[illegible]; S,3.5.2%.

Example 3

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-4-acridinecarboxamide

A mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid ([illegible]g) and 1-hydroxybenzotriazole (0.5g) in DMF (30ml) was stirred at room temperature for 10min. Intermediate 2(a) (1.27g) in DMF (20ml) was then added, followed by

cyclohexylcarbodiimide (0.70g) and the mixture was stirred at room temperature for 18hours and filtered. The filtrate was concentrated in vacuo, the residue dissolved in sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated to give a residue which was purified by column chromatography eluting with dichloromethane:methanol (97: The solid was recrystallised from isopropanol and filtered off to give the title compound (0.89g), mp 190°C

Analysis Found: C,68.6; H,5.9; N,

$C_{35}H_{35}N_3O$ requires: C,68.6; H,6.1; N,

Example

5-Fluoro-9,10-dihydro-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6-methoxy-7-methoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide

A mixture of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1.1g) and 1-hydroxybenzotriazole (0.5g) in DMF (30ml) was stirred at room temperature for 15 min. Intermediate 2(b) (1.4g) in DMF (20ml) was then added followed by cyclohexylcarbodiimide (0.8g) and the mixture was stirred at room temperature for 18hours and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated to give a residue which was purified by column chromatography eluting with dichloromethane:methanol (97: The solid was crystallised from isopropanol and filtered off to give the title compound (0.28g), mp 252°C

Analysis Found: C,66.1; H,5.4; N,6.8; S

$C_{44}H_{42}FN_5O_4S$ requires: C,66.3; H,5.6; N,6.9; S,

The following compounds were prepared in a similar manner to Example to 4

Example

9,10-Dihydro-5-methyl-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (Intermediate 2(b)) (1.4g) gave, after crystallisation from isopropanol, the title compound (0.9g), m.p. 155°.

Analysis Found: C,68.8; H,5.9; N,6.3; S,5.0;

$C_{35}H_{35}N_3O_4S.H_2O$ requires: C,68.7; H,6.1; N,6.8; S,5.2%.

Example 6

9,10-Dihydro-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-7-methoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (Intermediate (a)) (1.1g) gave, after crystallisation from isopropanol, the title compound (0.7g), m.p. 220°.

Analysis Found: C,71.4; H,5.9; N,7.

$C_{34}H_{33}N_3O_3S.0.5H_2O$) requires: C,71.3; H,6.0; N,7.

Example 7

9,10-Dihydro-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-7-methoxy-2-isoquinolinyl)ethoxy]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid with Intermediate (a) (0.51g) gave, after crystallisation from isopropanol, the title compound (0.3g), m.p. 154°.

Analysis Found: C,70.4; H,5.7; N,7.

$C_{34}H_{31}N_3O_3.0.5H_2O$) requires: C,70.9; H,5.8; N,7.

Example 8

9,10-Dihydro-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-7-dimethylamino-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with intermediate 2(b) (1g) gave, after crystallisation from isopropanol the title compound (1.04g), m.p. 182°.

Analysis Found : C,67.3; H,5.6; N, 5.25;

$C_{34}H_{33}N_3O_4S(1.5H_2O)$ requires : C,67.3; H,5.9; N, 5.3%.

Example 9

9,10-Dihydro-5-methyl-9-oxo-N-[4-[4-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)butyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (1g) with intermediate 2(d) (1.34g) gave, after crystallisation from ethanol / acetone, the title compound (0.86g), m.p. 140°.

Analysis Found : C,73.1; H,6.3; N, 4.

$C_{36}H_{37}N_3O_6$ (H_2O) requires : C,72.8; H,6.5; N, 7.1%.

Example 10

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.65g) with intermediate 5(b) (0.53g) gave, after crystallisation from isopropanol, the title compound (0.3g), m.p. 135°.

Analysis Found : C,70.9; H,6.0; N, 4.

$C_{35}H_{35}N_3O_6$ (H_2O) requires : C,70.6; H,6.3; N, 7.0%.

Example 11

9,10-Dihydro-5-methyl-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (0.61g) with intermediate 5(b) (0.53g) gave, after crystallisation from isopropanol, the title compound (0.45g), m.p. 120°.

Analysis Found : C,73.2; H,6.15; N, 4.

$C_{3}H_{35}N_{}O_{}$ (0.5 H_2O) requires : C,73.7; H,6.35; N.

Example 12

5-Fluoro-9,10-dihydro-9-oxo-N-[4-[2-(1,2,3,4-tetrah o-6,7-di e xy -
isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acr carboxy c g) with Intermediate 2(c) (0.81g) gave, after c allisa c m acetonitrile/isopropanol (1:1), the title compound (0.2g), m. 12$0^{0}$.

Analysis Found : C,69.4; H,5.2; N,7.

$C_{3}H_{30}FN_{}$ (H_2O) requires : C,69.6; H,5.6; N 7.

Example 13

5-Fluoro-9,10-dihydro-9-oxo-N-[4-[3-(1,2,3,4-tetrah -6,7-di e xy -
isoquinolinyl ropyl]phenyl]-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acr carboxy c g) with Intermediate 5(b) (0.85g) gave, after crystallisation from isopropa ol he title compound (0.4g), m.p. 166^{0}.

Analysis Found : C,70.3; H,5.4; N,

$C_{}H_{32}F$ (H_2O) requires : C,69.9; H,5.8; N,

Example 14

9,10-Dihydro-5-methyl-9-oxo-N-[4-[2-(1,2,3,4-tetra -6,7-di e xy -
isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4 linecarb x id (0.63g) with Intermediate 2(c) (0.62g) gave, after crystal ion from et he title compound (0.2g), m.p. 175^{0}.

Analysis Found : C,71.8; N,6.2; N,7

$C_{}H_{3}$ H_2O requires: C,72.2; H,6.2; N,7

Example

[illegible]1[illegible]-D[illegible]ydro-N-[2-methoxy-4-[3-(1,2,3,4-tetra[illegible]o-6,7-[illegible]in[illegible]oxy-2-[illegible]oquinolinyl)propyl]phenyl]-5-methyl-9-oxo-4-acridine[illegible]carboxamide

A mixture of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic a[illegible](1[illegible]) and 1-hydroxybenzotriazole (0.53g) in DMF (30ml) was stirred at room temperature for 1h. An intermediate 16(a) (1.28g) in DMF (20ml) was then added followed by cyclohexylcarbodiimide (0.74g) and the mixture was stirred at room temperature for 16h. It was then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with dichloromethane. The organic layer was then washed with water, dried and concentrated to give a residue which was purified by column chromatography eluting with dichloromethane:methanol (95:5) to give a solid which was recrystallised from ethyl acetate to give the title compound (0.5g), m.p. 174°

Analysis:	Found:	C,72.9; H,6.3; N,[illegible]4
$C_{36}H_{37}N_3O_5$ requires:		C,73.1; H,6.3; N,[illegible]

Example

[illegible]-[illegible]-5-[illegible]ethoxy-N-[2-methoxy-4-[3-(1,2,3,4-[illegible]a[illegible]dro-6,7-[illegible]di[illegible]hoxy-2-[illegible]oquinolinyl)propyl]phenyl]-9-oxo-4-acridinecarboxa[illegible]

A solution of Intermediate 16(a) (1.28g) and cyclohexylcarbodiimide (0.74g) in DMF (20ml) was added to a stirred solution of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1g) and 1-hydroxybenzotriazole (0.5[illegible]) in DMF (30ml). The resulting mixture was stirred overnight at room temperature, filtered and concentrated in vacuo. The residue was taken up in dichloromethane and then washed successively with dilute sodium hydroxide solution and water. The organic layer was then dried and evaporated to give a residue which was purified by column chromatography eluting with dichloromethane:methanol (95:5) to give a solid which was recrystallised from ether to give the title compound (0.[illegible]g), m.p. 18[illegible]°

Analysis:	Found:	C,70.9; H,[illegible]
$C_{36}H_{37}N_3O_6$ requires:		C,71.15; H,[illegible]

The following compounds were prepared in a similar manner to Examples 15 and 16.

Example 17

5-Fluoro-9,10-dihydro-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.31g) with Intermediate 8(a) (0.4g) gave, after crystallisation from isopropanol, the title compound (0.2g), m.p. 152^0.

Analysis Found : C,65.7; H,5.6; F,3.0; N,6.9;

$C_{35}H_{34}FN_3O_6$ (1.5 H_2O) requires : C,65.8; H,5.8; F,2.9; N,6.6%.

Example 18

9,10-Dihydro-5-methoxy-N-[2-methyl-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.5g) with Intermediate 8(b) (1.3g) gave, after crystallisation from isopropanol/ethanol, the title compound (0.53g), m.p. 160^0.

Analysis Found : C,69.6; H,5.8; N,6.5;

$C_{36}H_{37}N_3O_6(0.5H_2O)$ requires : C,70.1; H,6.2; N,6.8%.

Example 19

9,10-Dihydro-5-methyl-N-[2-methyl-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 8(b) (1.4g) gave, after crystallisation from acetone, the title compound (0.73g), m.p. 160^0.

Analysis Found : C,71.0; H,6.1; N,6.5;

$C_{36}H_{37}N_3O_5$ (H_2O) requires : C,70.9; H,6.4; N,6.9%.

Example 20

9,10-Dihydro-5-methoxy-N-[2-methyl-4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.7g) with Intermediate 16(c) (1.7g) gave, after crystallisation from ethanol, the title compound (0.21g), m.p. 200-201^0.

Analysis Found: C,71.9; H,5.9; N,6.9;

$C_{35}H_{35}N_3O_5(O.5H_2O)$ requires : C,71.65; H,6.2; N,7.2%.

Example 21

5-Fluoro-9,10-dihydro-N-[2-methyl-4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 16(c) (1.25g) gave, after crystallisation from ethanol, the title compound (0.32g), m.p. 210^0.

Analysis Found : C,71.2; H,5.9; F,3.4; N,7.4;

$C_{34}H_{32}FN_3O_4$ (0.5 H_2O) requires : C,71.1; H,5.8; F,3.3; N,7.3%.

Example 22

9,10-Dihydro-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (0.7g) with Intermediate 8(a) (1g) gave, after crystallisation from acetonitrile, the title compound (0.83g), m.p. 183-184^0.

Analysis Found : C,70.2; H,6.1; N,6.8;

$C_{36}H_{37}N_3O_6$ (0.5H_2O) requires : C,70.1; H,6.2; N,6.8%.

Example 23

N-[2-Ethoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.65g) with Intermediate 16(b) (0.6g) gave, after crystallisation from isopropanol/acetonitrile (9:1), the title compound (0.22g), m.p. 198^0.

Analysis Found : C,71.1; H,6.4; N,6.9:

$C_{37}H_{39}N_3O_6$ requires: C,71.5; H,6.3; N,6.8%.

Example 24

N-[2-Methoxy-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propoxy]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) and 1-hydroxybenzotriazole (0.5g) in DMF (30 ml) was stirred at room temperature for 10 min. Intermediate 22(b) (1.2g) in DMF (15 ml) was then added, followed by dicyclohexylcarbodiimide (0.8g) and the mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated and the residue was purified by column chromatography eluting with dichloromethane- methanol (97:3). The solid was recrystallised from isopropanol to give the title compound (0.68g). M.p. 108^0.

Analysis Found : C 66.4; H 5.5; F 3.0; N 7.0;

$C_{34}H_{34}FN_3O_6(H_2O)$ Requires : C 66.11; H 5.8; F 3.1; N 6.8%.

Example 25

N-[2-Methyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy] phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) and 1-hydroxybenzotriazole (0.47g) in DMF (30 ml) was stirred at room temperature for 10 min. Intermediate 22(a) (1.2g) in DMF (15 ml) was then added, followed by dicyclohexylcarbodiimide (0.7g) and the mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated and the residue was purified by column

chromatography eluting with dichloromethane- methanol (98:2). The solid was then recrystallised from isopropanol to give the title compound (0.86g). M.p. 130^0.

Analysis Found : C 69.93; H 5.89; F 3.2; N 7.3;

$C_{34}H_{34}FN_3O_5$ Requires : C 69.97; H 5.87; F 3.2; N 7.2%.

Example 26

N-[2-Methoxy-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

A mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1g) and 1-hydroxybenzotriazole (0.62g) in DMF (30ml) was stirred at room temperature for 10 min. Intermediate 22(b) (1g) in DMF (20 ml) was then added followed by dicyclohexylcarbodiimide (0.62g) and the mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with methylene chloride. The combined, dried organic extracts were evaporated and the residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol (97:3). After crystallization from isopropanol, the title compound was obtained as a solid (0.4 g). M.p. 146^0.

Analysis Found: C68.4; H5.9; N6.7;

$C_{35}H_{37}N_3O_7$ Requires: C68.7; H6.1; N6.9%.

In the same way, the following compounds were prepared :

Example 27

N-[2-Methyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy] phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridine carboxylic acid (1g) with Intermediate 22(a) (1.23g) gave, after crystallization from isopropanol, the title compound as a solid (1.2g). M.p. 146^0.

Analysis Found : C 72.5; H 6.5; N 7.1;

$C_{35}H_{37}N_3O_5$ Requires : C 72.5; H 6.4; N 7.2%.

Example 28

N-[2-Methyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.9g) with Intermediate 22(a) (1.2g) gave, after crystallization from isopropanol, the title compound as a solid (1.3g). M.p. 145-150^0.

NMR includes d 2.2 and 2.3 (2s,2x3H,N-CH_3 and CH_3-Ar), 3.4(s,2H,CH_2-Ar), 3.7(s,6H,OCH_3), 6.6-8.5(m,13H. aromatics).

Example 29

N-[2-Methyl-4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethoxy] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxylic acid (1.2g) with Intermediate 22(d) (1.12g) gave, after crystallization from ethanol, the title compound as a solid (0.6g). M.p. 178-179^0.

Analysis Found :	C 70.1; H 6.1; N 7.1;
$C_{34}H_{35}N_3O_6$ Requires :	C 70.2; H 6.1; N 7.2%.

Example 30

N-[2-Ethyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propoxy]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridine carboxylic acid (1g) with Intermediate 22(c) (1.2g) gave, after crystallization from isopropanol, the title compound as a solid (0.95g). M.p. 146^0.

Analysis Found :	C 70.3; H 6.1; F 3.2; N 7.0;
$C_{35}H_{36}FN_3O_5$ Requires :	C 70.3; H 6.1; F 3.1; N 7.0%.

Example 31

N-[2-Methoxy-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propoxy]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridine carboxylic acid (0.8g) with Intermediate 22(b) (1.14g) gave, after crystallization from isopropanol, the title compound as a solid (0.4g). M.p. 156-157^0.

Analysis Found : C 70.6; H 6.3; N 7.15;

$C_{35}H_{37}N_3O_6$ Requires : C 70.6; H 6.3; N 7,05%.

Example 32

N-[2-Methyl-4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl] phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridine carboxylic acid (0.82g) with Intermediate 27(a) (1.07g) gave, after crystallization from ethanol, the title compound as a yellow solid (0.21 g). M.p. 125^0.

Analysis Found : C 68.3; H 5.8; F 3.3; N 7.2;

$C_{33}H_{32}FN_3O_4$ (1.5 H_20) Requires : C 68.3; H 6.1; F 3.3; N 7.2%.

Example 33

N-[2-Methyl-4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino] ethyl]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridine carboxylic acid (0.8g) with Intermediate 27(a) (1g) gave, after crystallization from ethanol, the title compound as a yellow solid (0.45g). M.p. 160-161^0.

Analysis Found : C 73.4; H 6.3; N 7.5;

$C_{34}H_{35}N_3O_4$ (0.5 H_20) Requires: C 73.1; H 6.5; N 7.5%.

Example 34

N-[2-Methoxy-4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino] ethyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridine carboxylic acid (1g) with Intermediate 27(b) (1.3g) gave, after crystallization from ethanol, the title compound as a solid (0.55g). M.p. 161-162^0.

Analysis Found: C69.3; H5.8; N7.5;

$C_{33}H_{32}FN_3O_5$ Requires: C69.6; H5.6; N7.4%

Example 35

N-[2-Methyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxylic acid (0.69g) with Intermediate 27(c) (0.65g) gave, after crystallization from isopropanol, the title compound as a solid (0.185g). M.p. 154^0.

Analysis Found : C 72.65; H 6.4; N 7.0;

$C_{35}H_{37}N_3O_5$ Requires : C 72.5; H 6.4; N 7.25%.

Example 36

N-[2-Methyl-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridine carboxylic acid (0.5g) with Intermediate 27(c) (0.59g) gave, after crystallization from isopropanol, the title compound as a solid (0.26 g). M.p. 132^0.

Analysis Found : C 71.9; H 6.0; F 3.3; N 7.3;

$C_{34}H_{34}FN_3O_4$ Requires : C 71.9; H 6.0; F 3.3; N 7.45%.

Example 37

N-[2-Methoxy-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxylic acid (0.43g) and Intermediate 30 (0.5g) gave, after crystallization from isopropanol, the title compound as a solid (0.16g). M.p. 105^0.

Analysis Found : C 70.6; H 6.3; N 6.9;

$C_{35}H_{37}N_3O_6$ Requires : C 70.6; H 6.3; N 7.0%.

Example 38

N-[2-Methoxy-4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino] propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridine carboxylic acid (0.4g) with Intermediate 30 (0.5g) gave, after crystallization from ethanol/cyclohexane, the title compound as a solid (0.26 g). m.p. 170-190^0.

Analysis Found: C67.7; H5.7; N6.6;

$C_{34}H_{34}FN_3O_5,H_2O$ Requires: C67.9; H6.0; N7.0%.

Example 39

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.42 g) and 1-hydroxybenzotriazole (0.27 g) in DMF (30 ml) was stirred at room temperature for 10 min. Intermediate 33(a) (0.55g) in DMF (30 ml) was then added, followed by dicyclohexylcarbodiimide (0.34 g), and the mixture was stirred at room temperature for 16h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution, and extracted with dichloromethane. The combined, dried, organic extracts were evaporated to leave an oil which was purified by column chromatography eluting with dichloromethane/methanol (95:5) to give an oil which was crystallised from ethanol and filtered off to give the title compound (0.32g), MP : 131^0.

Analysis Found : C,71.4;H,5.9;N,7.3;

$C_{34}H_{34}FN_3O_4$ Requires : C,71.9;H,6.0;N,7.4%.

Example 40

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

A mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) and 1-hydroxybenzotriazole (0.41 g) in DMF (50 ml) was stirred at room temperature for 10 min. Intermediate 33(b) (0.9g) in DMF (30 ml) was then added, followed by dicyclohexylcarbodiimide (0.62 g), and the mixture was stirred at room

temperature for 16h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution, and extracted with dichloromethane. The combined, dried, organic extracts were evaporated to leave an oil which was purified by column chromatography eluting with dichloromethane/methanol (95:5) to give a solid. This was crystallised from isopropanol and filtered off to give the title compound (0.31g), MP: 172^0.

Analysis Found :	C,71.3;H,6.0;N,7.35;
$C_{33}H_{33}N_3O_5$ Requires :	C,71.8;H,6.0;N,7.6%.

Example 41

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (4 g) and 1-hydroxybenzotriazole (2.83 g) in DMF (50 ml) was stirred at room temperature for 10 min. Intermediate 33(a) (5.5g) in DMF (100 ml) was then added, followed by dicyclohexylcarbodiimide (3.45 g), and the mixture was stirred at room temperature for 16h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution, and extracted with dichloromethane. The combined, dried, organic extracts were evaporated to leave an oil which was purified by column chromatography eluting with dichloromethane/methanol (95:5) to give a solid. This was crystallised from methanol and then filtered off to give the title compound (3.2 g), MP : 140^0.

Analysis Found :	C,74.3;H,6.5;N,7.7;
$C_{34}H_{35}N_3O_4$ Requires:	C,74.3;H,6.4;N,7.6%.

Example 42

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) and 1-hydroxybenzotriazole (0.56 g) in DMF (50 ml) was stirred at room temperature for 10 min. Intermediate 33(b) (1g) in DMF (10 ml) was then added followed by

dicyclohexylcarbodiimide (0.7 g).The mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with dichloromethane. The combined, dried organic extracts were evaporated to leave an oil which was purified by column chromatography eluting with dichloromethane/methanol (9:1) to give a solid. This solid was crystallised from acetonitrile and filtered off to give the title compound (0.35 g), MP : 172^0.

Analysis Found :	C,73.6;H,6.0;N,8.0;
$C_{32}H_{31}N_3O_4$ Requires :	C,73.7;N,6.0;N,8.1%.

The following compounds were prepared in a similar manner to Examples 39 to 42 :

Example 43

N-[4-[[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8g) with Intermediate 38(d) (1.16g) gave, after crystallisation from ethanol, the title compound (0.28g), MP : 140^0.

Analysis Found :	C,69.7;H,5.7;N,7.5;
$C_{33}H_{33}N_3O_4S$ Requires :	C,69.8;H,5.9;N,7.4 %.

Example 44

N-[4-[2-[(Phenylmethyl)methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1 g) with Intermediate 36(c) (1g) gave, after crystallisation from ethanol, the title compound (0.8g), MP : 173^0.

Analysis Found :	C,75.5;H,5.6;N,8.8;
$C_{30}H_{27}N_3O_3$ Requires :	C,75.45;H,5.7;N,8.8 %.

Example 45

N-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1 g) with Intermediate 38(a) (1.44 g) gave, after crystallisation from ethanol, the title compound (0.82 g), MP : 140^0.

Analysis Found :	C,71.7;H,6.3;N,7.4;
$C_{34}H_{35}N_3O_5$ Requires :	C,72.2;H,6.2;N,7.4 %.

Example 46

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (2g) with Intermediate 38(c) (2.4g) gave, after crystallisation from isopropanol, the title compound (1.2g), MP : 180^0.

Analysis Found :	C,70.1; H,6.1; N,7.2;
$C_{34}H_{35}N_3O_6$ requires :	C,70.2; H,6.1; N,7.2%.

Example 47

N-[4-[2-[[2-(4-Methoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 36(e) (0.9g) gave, after crystallisation from ethanol, the title compound (0.7g),MP : 165^0.

Analysis Found :	C,73.6;H,6.0;N,8.0;
$C_{32}H_{31}N_3O_4$ Requires :	C,73.7;H,6.0;N,8.1%.

Example 48

N-[4-[3-[[2-(4-Methoxyphenyl)ethyl]methylamino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 38(b) (0.94 g) gave, after crystallisation from ethanol, the title compound (0.9 g), MP : 160^0.

Analysis Found : C,73.9;H,6.2;N,7.8;

$C_{33}H_{33}N_3O_4$ Requires : C,74.0;H,6.2;N,7.8 %.

Example 49

N-[4-[2-[[(4-Methoxyphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.6 g) with Intermediate 36(f) (0.72 g) gave, after crystallisation from methanol, the title compound (0.18 g), MP : 146^0.

Analysis Found : C,73.5;H,5.8;N,8.1;

$C_{31}H_{29}N_3O_4$ Requires : C,73.35;H,5.8;N,8.3 %.

Example 50

N-[4-[2-[[(4-Methylphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.7 g) with Intermediate 36(g) (0.78 g) gave, after crystallisation from isopropanol, the title compound (0.23 g), MP : 168^0.

Analysis Found : C,75.3;H,6.0;N,8.1;

$C_{31}H_{29}N_3O_3$ Requires : C,75.7;H,5.95;N,8.55 %.

Example 51

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1 g) with Intermediate 36(b) (1.25 g) gave, after crystallisation from ethanol, the title compound (1.39 g), MP : 140^0.

Analysis Found : C,71.7;H,6.2;N,7.7;

$C_{32}H_{31}N_3O_5$ Requires : C,71.5;H,5.8;N,7.8%.

Example 52

N-[4-[2-[[[4-(Methylthio)phenyl]methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 36(h) (1 g) gave, after crystallisation from ethanol, the title compound (0.75 g), MP : 150^0.

Analysis Found : C,71.1;H,5.6;N,7.9;S,5.8; $C_{31}H_{29}N_3O_3S$

Requires : C,71.1;H,5.6;N,8.0;S,6.1 %.

Example 53

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-2-(methylthio)-9-oxo-4-acridinecarboxamide

The coupling of Intermediate 39 (0.7 g) with Intermediate 36(b) (0.81 g) gave, after crystallisation from ethanol, the title compound (0.45 g), MP : 170^0.

Analysis Found : C,68.1;H,5.65;N,7.0;S,5.4; $C_{33}H_{33}N_3O_5S$

Requires : C,67.9;H,5.7;N,7.2;S,5.5%.

Example 54

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-7-(methylthio)-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-7-(methylthio)-9-oxo-4-acridinecarboxylic acid (0.7 g) with Intermediate 36(b) (0.81g) gave, after crystallisation from acetonitrile, the title compound (0.14 g), MP : 160^0.

Analysis Found : C,67.8;H,5.8;N.7.1;S,5.4; $C_{33}H_{33}N_3O_5S$

Requires : C,67.9;H,5.7;N,7.2;S,5.5 %.

Example 55

N-[4-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-2-(methylthio)-9-oxo-4-acridinecarboxamide

The coupling of Intermediate 39 (0.8g) with Intermediate 36(a) (0.93 g) gave, after crystallisation from ethanol the title compound (0.46 g), MP : 150^0.

Analysis Found : C,68.0;H,5.8;N,7.0;S,5.1; $C_{34}H_{35}N_3O_5S$

Requires : C,68.3;H,5.9;N,7.0;S,5.4 %.

Example 56

N-[4-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]ethoxy)phenyl]-9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxylic acid (0.72g) with Intermediate 36(a) (0.9g) gave, after crystallisation from isopropanol, the title compound (0.8g), MP : 139^0.

Analysis Found : C,72.25; H,6.2; N,7.4;

$C_{34}H_{35}N_3O_5$ Requires : C,72.2; H,6.2; N,7.4%.

Example 57

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-acridinecarboxylic acid (0.8 g) with Intermediate 36(b) (0.94 g) gave, after crystallisation from ethanol, the title compound (0.25 g), MP : 184^0.

Analysis Found : C,69.9;H,6.0;N,7.4;

$C_{33}H_{33}N_3O_6$ Requires : C,69.8;H,5.9;N,7.4 %.

Example 58

N-[4-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 36(a) (0.98 g) gave, after crystallisation from ethanol the title compound (0.25 g), MP : 190^0.

Analysis Found : C,70.0;H,6.1;N,7.3;

$C_{34}H_{35}N_3O_6$ Requires : C,70.2;H,6.1;N,7.2 %.

Example 59

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1 g) with Intermediate 38(c) (1.4 g) gave, after crystallisation from ethanol, the title compound (0.8g), MP : 130^0. IR includes signals at 1650 (CONH), 1620 (CO) and 3350cm^{-1} (NH).

Example 60

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 38(c) (1g) gave, after crystallisation from ethanol, the title compound (0.52 g), MP : 150^0.

Analysis Found : C,69.6;H,5.7;F,3.25;N,7.3; $C_{33}H_{32}FN_3O_5$

Requires : C,69.6;H,5.7;F,3.3;N,7.4 %.

Example 61

N-[4-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.76 g) with Intermediate 33(e) (1g) gave, after crystallisation from acetonitrile, the title compound (0.7g), MP : 180^0.

Analysis Found : C,73.5;H,6.1;N,7.9;

$C_{33}H_{33}N_3O_4$ Requires : C,74.0;H,6.2;N,7.8 %.

Example 62

N-[4-[4-[[[4-(Methylthio)phenyl]methyl]methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(j) (1 g) gave, after crystallisation from acetonitrile, the title compound (0.64g), MP : 135^0.

Analysis Found : C,73.7;H,6.2;N,7.9;S,5.7; $C_{33}H_{33}N_3O_2S$

Requires : C,74.0;H,6.2;N,7.8;S,6.0 %.

Example 63

N-[4-[4-[[(4-Fluorophenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.7 g) with Intermediate 33(i) (0.86 g) gave, after crystallisation from acetonitrile, the title compound (0.43 g), MP : 151^0.

Analysis Found : C,75.9;H,6.0;F,3.7;N,8.25; $C_{32}H_{30}FN_3O_2$

Requires : C,75.7;H,5.9;F,3.7;N,8.3 %.

Example 64

N-[4-[3-[[(4-Methoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.72 g) with Intermediate 33(g) (0.85 g) gave, after crystallisation from isopropanol, the title compound (0.64 g), MP : 155^0.

Analysis Found : C,76.2;H,6.1;N,7.9;

$C_{32}H_{31}N_3O_3$ Requires : C,76.0;H,6.2;N,8.3%.

Example 65

N-[4-[4-[[2-(4-Methoxyphenyl)ethyl]methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(h) (1 g) gave, after crystallisation from acetonitrile, the title compound (0.53 g), MP : 143^0.

Analysis Found : C,76.4;H,6.6;N,7.8;

$C_{34}H_{35}N_3O_3$ Requires : C,76.5;H,6.6;N,7.9 %.

Example 66

N-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(d) (1 g) gave, after trituration with ether, the title compound (0.88 g), MP : 114^0.

Analysis Found : C,74.2;H,6.35;N,7.55;

$C_{34}H_{35}N_3O_4$ Requires : C,74.3;H,6.4;N,7.6 %.

Example 67

N-[4-[4-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.72 g) with Intermediate 33(c) (1 g) gave, after crystallisation from acetonitrile, the title compound (0.12 g), MP : 120^0.

Analysis Found : C,74.2;H,6.5;N,7.6;

$C_{35}H_{37}N_3O_4$ Requires : C,74.6;H,6.6;N,7.45 %.

Example 68

N-[4-[2-[[2-(4-Methoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(k) (0.95 g) gave, after crystallisation from acetonitrile, the title compound (0.4 g), MP : 179^0.

Analysis Found : C,76.0;H,6.1;N,8.1;

$C_{32}H_{31}N_3O_3$ Requires : C,76.0;H,6.2;N,8.3 %.

Example 69

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(f) (1 g) gave, after crystallisation from acetonitrile, the title compound (1 g), MP : 112^0.

Analysis Found :	C,74.1;H,6.2;N,7.7;
$C_{33}H_{33}N_3O_4$ Requires :	C,74.0;H,6.2;N,7.8 %.

Example 70

N-[4-[5-[[(3,4-Dimethoxyphenyl)methyl]methylamino]pentyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(l) (1.15 g) gave, after trituration with ether, the title compound (0.41 g), MP : 110^0.

Analysis Found :	C,74.3;H,6.6;N,7.4;
$C_{35}H_{37}N_3O_4$ Requires :	C,74.6;H,6.6;N,7.45 %.

Example 71

N-[4-[4-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]butyl]phenyl]-9,10-dihydro-7-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-7-methoxy-9-oxo-4-acridinecarboxylic acid (1 g) with Intermediate 33(c) (1.3 g) gave, after crystallisation from ethanol, the title compound (0.85 g), MP : 155^0.

Analysis Found :	C,72.7;H,6.9;N,7.05;
$C_{36}H_{39}N_3O_5$ Requires :	C,72.8;H,6.6;N,7.1 %.

Example 72

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(a) (0.98 g) gave, after crystallisation from isopropanol, the title compound (0.12 g), MP : 157^0.

Analysis Found : C,71.9;H,6.4;N,7.2;

$C_{35}H_{37}N_3O_5$ Requires : C,72.5;H,6.4;N,7.25 %.

Example 73

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.72 g) with Intermediate 33(f) (0.9g) gave, after crystallisation from ethanol, the title compound (0.89 g), MP : 158^0.

Analysis Found : C,71.9;H,6.1;F,3.25;N,7.7; $C_{33}H_{32}FN_3O_4$

Requires : C,71.65;H,5.8;F,3.4;N,7.6 %.

Example 74

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 33(b) (1.2 g) gave, after crystallisation from ethanol, the title compound (0.78 g), MP : 175^0.

Analysis Found : C,69.9;H,5.5;F,3.1;N,7.45; $C_{32}H_{30}FN_3O_4$ (0.5 H_2O) Requires : C,70.1;H,5.7;F,3.5;N,7.65%.

Example 75

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxylic acid (0.6g) with Intermediate 33(a) (0.7 g) gave, after crystallisation from acetonitrile, the title compound (0.35 g), MP : 174^0.

Analysis Found : C,68.6;H,5.7;N,9.5;

$C_{34}H_{34}N_4O_6$ Requires : C,68.7;H,5.8;N,9.4 %.

Example 76

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxylic acid (0.6 g) with Intermediate 33(b) (0.63 g) gave, after crystallisation from isopropanol, the title compound (0.45 g), MP : 197°.

Analysis Found : C,67.4;H,5.3;N,9.7;

$C_{32}H_{30}N_4O_6$ Requires : C,67.8;H,5.3;N,9.9 %.

Example 77

N-[4-[5-[[(3,4-Dimethoxyphenyl)methyl]methylamino]pentyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(l) (1 g) gave, after crystallisation from acetonitrile, the title compound (0.29 g), MP : 130°.

Analysis Found : C,71.9;H,6.2;F,3.2;N,7.1; $C_{35}H_{36}FN_3O_4$

Requires : C,72.3;H,6.2;F,3.3;N,7.2 %.

Example 78

N-[4-[4-[[2-(4-Methoxyphenyl)ethyl)methylamino]butyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(h) (0.93 g) gave, after trituration with ether, the title compound (0.31 g), MP : 182°.

Analysis Found : C,74.2;H,6.6;N,7.8;

$C_{35}H_{37}N_3O_4$ Requires : C,74.6;H,6.6;N,7.5 %.

Example 79

N-[4-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(e) (0.94 g) gave, after crystallisation from isopropanol, the title compound (0.17 g), MP : 179^0.

Analysis Found : C,72.3;H,6.0;N,7.8;

$C_{34}H_{35}N_3O_5$ Requires : C,72.2;H,6.2;N,7.4 %.

Example 80

N-[4-[4-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]butyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(c) (1 g) gave, after crystallisation from isopropanol, the title compound (0.12 g), MP : 170^0. IR gave signals at 1645 (CONH), 1620 (CO) and 3300cm^{-1} (NH).

Example 81

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-nitro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(f) (0.88 g) gave, after crystallisation from isopropanol, the title compound (0.29 g), MP : 192^0.

Analysis Found : C,67.8;H,5.6;N,9.4;

$C_{33}H_{32}N_4O_6$ Requires : C,68.3;H,5.6;N,9.65 %.

Example 82

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(f) (0.93 g) gave, after crystallisation from ethanol, the title compound (0.27 g), MP : 180^0.

Analysis Found :	C,72.0;H,6.1;N,7.6;
$C_{34}H_{35}N_3O_5$ Requires :	C,72.2;H,6.2;N,7.4 %.

Example 83

N-[4-[2-[(Phenylmethyl)ethylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 36(i) (0.9 g) gave, after crystallisation from ethanol, the title compound (0.34 g), MP : 157^0.

Analysis Found :	C,75.3;H,5.9;N,8.4;
$C_{31}H_{29}N_3O_3$ Requires :	C,75.7;H,5.9;N,8.5 %.

Example 84

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxylic acid (0.8 g) with Intermediate 33(a) (1.04 g) gave, after crystallisation from isopropanol, the title compound (0.65 g), MP : 142^0. IR gave signals at 1675 (CONH), 1610 (CO) and 3250cm^{-1} (NH).

Example 85

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-10-methyl-9-oxo-4-acridinecarboxylic acid (0.87 g) with Intermediate 33(b) (1g) gave, after crystallisation from isopropanol, the title compound (0.42 g), MP : 182^0.

Analysis Found :	C,73.5;H,6.1;N,7.8;
$C_{33}H_{33}N_3O_4$ Requires :	C,74.0;H,6.2;N,7.8 %.

Example 86

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-7-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-7-methoxy-9-oxo-4-acridinecarboxylic acid (0.8g) with Intermediate 33(a) (0.97g) gave, after crystallisation from isopropanol, the title compound (0.17g), MP : 172^0.

Analysis Found : C,71.5; H,6.4; N,6.9;

$C_{35}H_{37}N_3O_5$, $0.5H_2O$ Requires : C,71.4; H,6.5; N,7.1%.

Example 87

N-[4-[[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.7g) with Intermediate 36(d) (1g) gave, after crystallisation from isopropanol, the title compound (0.26g), MP : 113^0.

Analysis Found : C,69.3; H,5.5; N,7.4; S,5.8;

$C_{32}H_{31}N_3O_4S$ Requires : C,69.4; H,5.6; N,7.6; S,5.8%.

Example 88

N-[4-[[3[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (0.8g) with Intermediate 38(d) (1.09g) gave, after crystallisation from ethanol, the title compound (50mg), MP : 158^0.

Analysis Found : C,69.4; H,5.9; N,6.9; S,5.6;

$C_{34}H_{35}N_3O_4S$, $0.5\ H_2O$ Requires : C,69.1; H,6.1; N,7.1; S,5.4%.

Example 89

N-[4-[[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 38(d) (1.28g) gave, after crystallisation from acetonitrile, the title compound (0.37g), MP : 184-186^0.

Analysis Found : C,68.1; H,5.9; N,6.8; S,5.2;

$C_{34}H_{35}N_3O_5S$ Requires : C,68.3; H,5.9; N,7.0; S,5.4%.

Example 90

N-[4-[[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-fluoro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-fluoro-9-oxo-acridinecarboxylic acid (0.9g) with Intermediate 38(d) (1.1g) gave, after crystallisation from isopropanol, the title compound (0.5g), MP : 120-130^0.

Analysis Found : C,66.6; H,5.6; F,3.1; N,6.9; S,5.3;

$C_{33}H_{32}FN_3O_4S$,0.5 H_2O Requires : C,66.6; H,5.6; F,3.2; N,7.1; S,5.4%.

Example 91

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methylthio-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methylthio-9-oxo-4-acridinecarboxylic acid (0.7g) with Intermediate 33(b) (0.74g) gave, after crystallisation from ethanol, the title compound (0.3g), MP : 190^0.

Analysis Found : C,68.5; H,6.1; N,7.2;

$C_{33}H_{33}N_3O_4S$, 0.5 H_2O Requires : C,68.7; H,5.9; N,7.3%.

Example 92

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (1.27g) with Intermediate 33(b) (1.5g) gave, after crystallisation from isopropanol/diisopropylether, the title compound (0.3g), MP : 119^0.

Analysis Found : C,73.5; H,6.2; N,7.6;

$C_{33}H_{33}N_3O_4$ Requires : C,74.0; H,6.2; N,7.8%.

Example 93

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 38(c) (1.3g) gave, after crystallisation from ispropanol, the title compound (0.9g), MP : 160°.

Analysis Found : C,72.3; H,6.3; N,7.5;

$C_{34}H_{35}N_3O_5$ requires : C,72.2; H,6.3; N,7.5%.

Example 94

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethylamino] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.4g) with Intermediate 43 (1.4g) gave after crystallisation from isopropanol, the title compound (0.2g), MP : 196°.

Analysis Found : C,69.8; H,6.3; N,10.0;

$C_{33}H_{34}N_4O_5$ requires : C,69.9; H,6.1; N,9.9%.

Example 95

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5,8-dimethoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5,8-dimethoxy-9-oxo-4-acridine carboxylic acid (0.8g) with Intermediate 33(b) (0.67g) gave, after crystallisation from ethanol, the title compound (0.15g) MP : 196°.

Analysis Found : C,68.99; H,5.76; N,7.18;

$C_{34}H_{35}N_3O_6$, 0.5 H_2O Requires : C,69.13; H,6.14; N,7.11%.

Example 96

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5,7-dimethoxy-9-oxo-4-acridinecarboxamide

The coupling of Intermediate 44 (1.4g) with Intermediate 33(b) (1.2g) gave, after crystallisation from ethanol, the title compound (0.25g), MP > 260^0.

Analysis Found : C,70.09; H,6.35; N,7.01;

$C_{34}H_{35}N_3O_6$ Requires C,70.20; H,6.06; N,7.22%.

Example 97

N-[4-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-6,7,8-trimethoxy-9-oxo-4-acridinecarboxamide

The coupling of Intermediate 45 (0.6g) with Intermediate 33(b) (0.6g) gave, after crystallisation from isopropanol, the title compound (0.4g), MP : 158^0.

Analysis Found : C,68.69; H,6.32; N,6.40;

$C_{35}H_{37}N_3O_7$ Requires : C,68.72; H,6.10; N,6.87%.

Example 98

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]amino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of Intermediate 40 (0.5g) and 3,4-dimethoxybenzenemethanamine (0.5 g) was heated for 1 h at 140^0. Water was then added and the mixture was extracted with dichloromethane. The dried organic phase was concentrated to give a solid which was purified by column chromatography eluting with dichloromethane/methanol (9:1). The resulting solid was crystallised from benzene to give the title compound (50 mg), MP : 138-139^0.

Analysis Found : C,70.1;H,5.9;N,7.5;

$C_{32}H_{31}N_3O_5$ (0.5 H_2O) Requires : C,70.3;H,5.9;N,7.7%.

Example 99

Oxalate of N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino] butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A solution of Example 41 (0.55 g) and oxalic acid dihydrate (0.126 g) in ethanol (10 ml) was boiled for 2 min. After cooling and scratching, crystallisation took place. The crystals were filtered off and dried to afford the title compound (0.55 g), MP : 155-160^0.

Analysis Found : C,66.3;H,5.9;N,6.3;

$C_{36}H_{37}N_3O_8$ (0.5 H_2O) Requires : C,66.6;H,5.9;N,6.4%.

Example 100

Maleate of N-[4-[4-[[(3,4-dimethoxyphenyl)methyl] methylamino]butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A solution of Example 41 (0.55 g) and maleic acid (0.130 g) in ethanol (50 ml) was boiled for 2 min. After cooling and scratching, crystallisation took place. The crystals were filtered off and dried to afford the title compound (0.5 g), MP : 205^0.

Analysis Found : C,68.2;H,5.9;N,6.2;

$C_{38}H_{39}N_3O_8$ Requires : C,68.5;H,5.9;N,6.3%.

Example 101

Hydrochloride of N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino] butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A hot solution of Example 41 (0.55 g) in ethanol (50 ml) was treated with a slight excess of an ethereal solution of hydrochloric acid. The solution was then concentrated to give a foam which was triturated with isopropanol to afford the title compound (0.4 g) as crystals, MP : 165^0.

Analysis Found : C,67.6;H,6.3;N,7.0;

$C_{34}H_{36}ClN_3O_4 . H_2O$ Requires : C,67.5;H,6.4;N,7.0%.

Example 102

L+ lactate of N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino] butyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A solution of Example 41 (0.55 g) and L+ lactic acid (0.95 g) in isopropanol (30 ml) was boiled for 2 min. After cooling and scratching, crystallisation took place. The crystals were filtered off and dried to afford the title compound (0.45 g), MP : 120^0.

Analysis Found : C,69.5;H,6.5:N,6.6;

$C_{37}H_{41}N_3O_7$ Requires : C,69.4;H,6.6;N,6.5%.

Example 103

Oxalate of N-[3-[3-[[(3,4-dimethoxyphenyl)methyl] methylamino]propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

A mixture of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) and 1-hydroxybenzotriazole (0.63g) in DMF (30ml) was stirred at room temperature for 10 min. Intermediate 51 (1.23g) in DMF (3.9ml) was then added followed by dicyclohexylcarbodiimide (0.8g) and the mixture was stirred at room temperature for 16 hours and then filtered. The filtrate was concentrated in vacuo, treated with dilute sodium hydroxide solution and extracted with methylene chloride. The combined, dried, organic extracts were evaporated to leave an oil which, after purified by column chromatography on silica gel eluting with methylene chloride/methanol (99:1), led to the title compound (1.1g), m.p. 126^0.

Analysis Found : C,63.9; H,5.4; F,2.8; N,6.2;

$C_{33}H_{32}F_1N_3O_4.C_2H_2O_4$ (H_2O) Requires : C,63.5; H,5.5; F,2.9; N,6.3%

The following compounds were prepared in a similar manner to Example 103 :

Example 104

N-[3-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.5g) with Intermediate 48(b) (1.22g) gave, after crystallisation from isopropanol, the title compound (0.47g) as a solid, m.p. 124^0.

Analysis Found : C,70.1; H,6.1; N,7.05;

$C_{34}H_{35}N_3O_6$ Requires : C,70.2; H,6.1; N,7.2%

Example 105

Oxalate of N-[3-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxylic acid (1.26g) with Intermediate 51 (1.23g) gave the title compound (1.13g), m.p. 112-114^0.

Analysis Found : C,65.2; H,6.2; N,6.2;

$C_{34}H_{35}N_3O_5.C_2H_2O_4$ (0.5 H_2O) Requires : C,65.0; H,5.8; N,6.3%

Example 106

Fumarate of N-[3-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino] ethyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.34g) with Intermediate 48(a) (0.4g) gave the title compound (0.3g), m.p. 155^0.

Example 107

Fumarate of N-[3-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino] ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.36g) with Intermediate 48(a) (0.4g) gave the title compound (0.13g), m.p. 140^0.

Example 108

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]butyl]-2-methoxyphenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.38g) with Intermediate 55 (0.5g) gave, after crystallisation from isopropanol, the title compound (0.36g) as a solid, MP : 114 - 115^0.

Analysis Found :	C,70.98; H,6.19; N,6.79;	$C_{36}H_{39}N_3O_6$
Requires :	C,70.92; H,6.45; N,6.89%.	

Example 109

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]amino]phenyl]-4-acridine-carboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.99g) with Intermediate 59 (1.2g) gave, after crystallisation from acetonitrile, the title compound (1.3g), MP : 228 - 234^0.

Analysis Found :	C,69.27; H,5.87; N,9.37;	
$C_{34}H_{34}N_4O_5$, $0.5H_2O$ Requires :	C,69.48; H,6.00; N,9.50%.	

Example 110

N-[4-[2-(2,3-Dihydro-5,6-dimethoxy-1H-isoindol-2-yl)ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.54g) with Intermediate 60 (0.6g) gave after crystallisation from ethanol, the title compound (0.3g), MP : 215 - 225^0. NMR includes signals at d 2.85(4H,s,N-$(CH_2)_2$-Ph); 3.7(6H,s,2xOMe); 3.8(3H,s,OMe); 3.9(4H,s,2xN-CH_2-Ph).

Example 111

9,10-Dihydro-5,8-dimethoxy-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5,8-dimethoxy-9-oxo-4-acridinecarboxylic acid (0.7g) with Intermediate 16(a) (0.83g) gave, after crystallisation from ethanol, the title compound (0.1g), MP : 140^0.

Analysis Found :	C,67.44; H,5.94; N,6.80;	
$C_{37}H_{39}N_3O_7$, H_2O Requires :	C,67.77; H,6.30; N,6.40%.	

Example 112

9,10-Dihydro-5-methoxy-N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-1-hydroxyethyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.49g) with Intermediate 63 (0.5g) gave, after crystallisation from acetonitrile, the title compound (0.8g), MP : 160-165^0.

Analysis Found : C,68.51; H,5.74; N,7.25;

$C_{34}H_{33}N_3O_6$, H_2O Requires : C,68.33; H,5.90; N,7.09%.

Example 113

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[[[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]methylamino]methyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.53g) Intermediate 67 (0.7g) gave, by precipitation from methylene chloride/diethyl ether, the title compound (0.5g), MP : 202^0.

Analysis Found : C,68.68; H,6.27; N,8.52;

$C_{36}H_{38}N_4O_5$, 1.25H_2O Requires : C,68.71; H,6.48; N,8.90%.

Example 114

N-[4-[[[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino]ethyl]methylamino]methyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.1g) with Intermediate 70 (1.43g) gave, after crystallisation from methanol, the title compound (0.75g) as yellow crystals, MP : 170^0.

Analysis Found : C,69.69; H,6.30; N,9.10;

$C_{35}H_{38}N_4O_5$,0.5 H_2O Requires : C,69.63; H,6.51; N,9.28%.

Example 115

5-Fluoro-9,10-dihydro-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.5g) with Intermediate 16(a) (0.63g) gave, after crystallisation from ethanol, the title compound (0.3g), MP : 128^0. NMR includes signals at d 3.6(3H,s,OMe); 3.8(6H,s,2xOMe); 9.15(1H,s,NHCO); 11.35(1H,s,NH acridone).

Example 116

N-[4-[[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-(methylthio)-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methylthio-9-oxo-4-acridinecarboxylic acid (0.3g) with Intermediate 38(d) (0.36g) gave, after crystallisation from methanol, the title compound (0.13g), MP : 142^0. NMR includes signals at d 2.2(3H,s,SMe); 2.45(3H,s,NMe); 3.7(6H,s,2xOMe).

Example 117

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]propyl]-2-methoxyphenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxylic acid (0.75g) and Intermediate 30 (1g) gave, after crystallisation from methanol, the title compound (0.1g), MP : 111^0. NMR includes signals at d 2.18(3H,s,NCH_3); 2.55(3H,s,CH_3 acridone); 3.42(2H,s,N-CH_2-Ph); 3.9(9H,3s,3xOMe).

Example 118

N-[2-Ethoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl) propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 16(b) (0.86g) gave, after crystallisation from acetonitrile, the title compound (0.4g), MP : 200^0. NMR includes signals at d 1,4(2H,t,CH_3-CH_2); 3,7(6H,s,2xOMe).

Example 119

N-[4-[4-[[(3,4-Dimethoxyphenyl)methyl]methylamino]-2-butenyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (154mg) with Intermediate 72 (210mg) gave, after crystallisation from ethanol, the title compound (80mg), MP : 140^0.

Analysis Found : C,74.17; H,6.08; N,7.61;

$C_{34}H_{33}N_3O_4$ Requires : C,74.55; H,6.07; N,7.67%.

Example 120

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]-1-propenyl] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.95g) with Intermediate 74 (1.1g) gave, after crystallisation from ethanol, the title compound (0.7g), MP : 200^0.

Analysis Found : C,72.46; H,6.04; N,7.61;

$C_{34}H_{33}N_3O_5$ Requires : C,72.45; H,5.90; N,7.45%.

Example 121

5-Methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6-methoxy-2-isoquinolinyl)ethyl]phenyl]-9,10-dihydro-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.5g) with Intermediate 76 (0.48g) gave, after crystallisation from pyridine/water, the title compound (0.4g), MP: 260^0.

Analysis Found : C,74.29;H,6.06;N,8.02; $C_{33}H_{31}N_3O_4$ requires : C,74.28;H,5.86;N,7.87%

Example 122

5-Fluoro-9,10-dihydro-9-oxo-N-[3-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 79 (1.3g) gave, after crystallisation from isopropanol, the title compound (0.25g), MP: 128°.

Analysis Found : C,68.84;H,5.67;F,3.01;N,6.88;

$C_{34}H_{32}FN_3O_4(1.5H_2O)$ requires : C,68.90;H,5.95;F,3.20;N,7.09%

Example 123

9,10-Dihydro-5-methoxy-9-oxo-N-[3-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.2g) with Intermediate 79 (1.2g) gave, after crystallisation from isopropanol, the title compound (0.5g), MP: 138-140°.

Analysis Found : C,70.55;H,6.25;N,7.06;

$C_{35}H_{35}N_3O_5(H_2O)$ requires : C,70.56;H,6.26;N,7.05%

Example 124

N-[4-[3-[[(3,4-Dimethoxyphenyl)methyl]methylamino]-2-hydroxypropoxy] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 81 (1.3g) gave, after crystallisation from isopropanol, the title compound (0.7g), MP: 175°.

Analysis Found : C,68.38;H,5.82;N,6.86; $C_{34}H_{35}N_3O_7$

requires : C,68.33;H,5.90;N,7.03%

Example 125

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[3-[[(3,4,5-trimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (1.5g) with Intermediate 83 (1.3g) gave, after crystallisation from isopropanol, the title compound (1.3g), MP:186°.

Analysis Found : C,68.82;H,6.08;N,6.83; $C_{35}H_{37}N_3O_7$
requires : C,68.72;H,6.10;N,6.87%

Example 126

Fumarate of 5-fluoro-9,10-dihydro-N-[2-methoxy-5-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1g) with Intermediate 86 (1.2g) gave the title compound (0.5g), MP: 166-168^0.

Analysis Found : C,63.78;H,5.15;N,6.10;
$C_{38}H_{36}FN_3O_9(H_2O)$ requires : C,63.76;H,5.35;N,5.87%

Example 127

9,10-Dihydro-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-2-isoquinolinyl)propoxy]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8g) with Intermediate 88 (0.9g) gave, after crystallisation from ethanol, the title compound (0.3g), MP: 182^0.

Analysis Found : C,74.88;H,5.81;N,8.16;
$C_{32}H_{29}N_3O_3(0.5H_2O)$ requires : C,74.98;H,5.90;N,8.20%

Example 128

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-7-methoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.7g) with Intermediate 90 (0.7g) gave, after crystallisation from isopropanol, the title compound (0.65g), MP: 213-216^0.

Analysis Found : C,73.27;H,5.94;N,7.82;
$C_{33}H_{31}N_3O_4(0.5H_2O)$ requires : C,73.04;H,5.94;N,7.74%

Example 129

9,10-Dihydro-5-methoxy-9-oxo-N-[3-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.5g) with Intermediate 92 (0.57g) gave, after crystallisation from isopropanol, the title compound (0.15g), MP: 152°.

Analysis Found : C,71.33;H,5.77;N,7.16;

$C_{34}H_{33}N_3O_5(0.5H_2O)$ requires : C,71.30;H,5.98;N,7.33%

Example 130

5-Fluoro-9,10-dihydro-9-oxo-N-[3-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.5g) with Intermediate 92 (0.57g) gave, after crystallisation from isopropanol, the title compound (0.35g), MP: 178°.

Analysis Found : C,70.80;H,5.36;F,3.34;N,7.34;

$C_{33}H_{30}FN_3O_4(0.5H_2O)$ requires : C,70.70;H,5.57;F,3.38;N,7.49%

Example 131

Fumarate of N-[5-[2-[[(3,4-Dimethoxyphenyl)methyl]methylamino] ethyl]-2-methoxyphenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide

The coupling of 5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxylic acid (0.8g) with Intermediate 95 (1g) gave the title compound (0.5g), MP: 140-142°.

Analysis Found : C,62.4;H,5.1;N,5.8;

$C_{37}H_{36}FN_3O_9(1.5H_2O)$ requires : C,62.35;H,5.5;N,5.9%

Example 132

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-5,6-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.19g) with Intermediate 97 (0.22g) gave, after crystallisation from pyridine/water, the title compound (0.32g), MP:235-237°. NMR includes signals at δ 2.6-3.0

(8H,m,2x N-$(CH_2)_2$-Ar), 3.6 (2H,s,N-CH_2-Ar), 3.75 (6H,bs,OCH_3), 4 (3H,s,OCH_3), 6.5-8.5 (12H,m,aromatics).

Analysis Found : C,72.38;H,5.80;N,7.41;

$C_{34}H_{33}N_3O_5$ requires : C,72.45;H,5.90;N,7.45%.

Example 133

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

The coupling of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (0.26g) with Intermediate 99 (0.3g) gave, after crystallisation from isopropanol, the title compound (0.3g), MP:222-226^0. NMR includes signals at d 2.4-2.9 (8H,m,2x N-$(CH_2)_2$-Ar), 3.45 (2H,s,N-CH_2-Ar), 3.7 (9H,bs,OCH_3), 3.9 (3H,s,OCH_3), 6.2-8.4 (11H,m,aromatics).

Analysis Found : C,69.46; H,6.14; N,6.84;

$C_{35}H_{35}N_3O_6$ (0.5 H_2O) requires: C,69.75; H,6.02; N,6.97%.

Example 134

5-Amino-N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide

A suspension of Example 75 (0.15g) in ethanol (40ml) was hydrogenated at room temperature in presence of 10% palladium-on- carbon (70mg). After the hydrogen absorption was completed, the mixture was diluted with methylene chloride (50ml). The catalyst was filtered off and the solution concentrated in vacuo to give the title compound (85mg) as a yellow solid, MP : 250^0.

Analysis Found : C,72.38; H,6.69; N,9.06;

$C_{34}H_{36}N_4O_4$ Requires : C,72.31; H,6.42; N,9.92%.

Example 135

9,10-Dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

Dicyclohexylcarbodiimide (22.76g) in DMF (50ml) was added dropwise to a stirred mixture of 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxylic acid (28.9g) and 1-hydroxybenzotriazole hydrate (15.66g) in DMF (300ml) maintained at 0^0, followed by Intermediate 101 (33.5g) in DMF (150ml). After 4 hours at 0^0 and 2 days at room temperature, the mixture was filtered, the filtrate was concentrated in vacuo and the residue taken up in 1N sodium hydroxide and extracted with dichloromethane. The organic layer was then washed with water, dried and evaporated to give a solid residue. This was dissolved in 500ml of boiling pyridine and the solution was clarified by filtration. The clear solution was diluted with 10ml of water and the product crystallised on cooling to give the title compound (52.82g). M.p. : 215-225^0.

NMR includes d 2.60-2.95 (m,8H,CH_2): 3.58 (s,2H,N-CH_2-Ph); 3.72 (s,6H,OMe); 4.05 (s,3H,OMe acridone); 6.78 (2s,2H,Ar.isoquinoline), 7.20-7.88 (m,8H,Ar.), 8.48 (t,2H,H_1 and H_8 acridone), 10.60 (s,1H,CONH), 12.32 (s,1H,NH acridone).

Analysis found : C,72.07; H,5.96; N,7.35;

$C_{34}H_{33}N_3O_5$ requires : C,72.45; H,5.90; N,7.45%.

Example 136

Maleate salt of 9,10-dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

Example 135 (100mg) was dissolved in 50ml of a mixture of dichloromethane and methanol (1:1) and maleic acid (22mg) was added. The mixture was boiled until a clear solution was obtained and the solution was evaporated in vacuo. The residue was taken up in hot methanol and cooled to give the title compound as yellow needles (90mg). M.P. : 171 to 187^0.

In the same way the following salts of Example 135 were prepared :

Fumarate :	m.p. : 170-203^0.
Succinate :	m.p. : 135-143^0.
L (+) Tartrate :	m.p. : 165-180^0.

Example 137

Hydrochloride salt of 9,10-dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide

Example 135 (100mg) was dissolved in a mixture of methanol and dichloromethane (4:1) and excess methanolic hydrogen chloride was added. The solvate was recovered which after addition of diethyl ether and filtration gave the title compound (ca. 100mg). MP 225^0 (softens with progressive loss of solvent).

Example 138

In vitro cytotoxicity of MDR inhibitors in Chinese Hamster Ovary cells

The multidrug resistant Chinese Hamster Ovary (CHO) cell line CH^RC5 was obtained from Dr V Ling, Princess Margaret Hospital, Toronto, Canada and maintained as anchorage-dependent monolayers in a-minimum essential medium supplemented with thymidine, adenosine, 10% fetal bovine serum, 2mM L-glutamine (Flow), 100 units/ml penicillin and 100mg/ml streptomycin in a humidified atmosphere of 95% air and 5% carbon dioxide. Cells were passaged into culture flasks twice a week after dissociation with EDTA.

CH^RC5 cells were seeded at a density of 10^4 cells/well in microtitre plates. After 24 hours, the medium was removed and replaced by 0.1ml of fresh medium containing successive two-fold dilutions of MDR inhibitors. Each MDR inhibitor was assayed in duplicate in two-fold dilution from 1250 to 20nM. The last well of each column was utilised to verify the lack of toxicity at the top dose of the MDR inhibitor in the absence of doxorubicin. Other control conditions were assayed on each microtitre plate : cells alone (1 well), doxorubicin alone (7 wells), amiodarone (a range of two-fold dilutions starting at 5mM; two wells each). 0.1ml of a 10mg/ml solution of doxorubicin was added. After 72 hours incubation cell viability was assessed by the reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT; Sigma) to a dark blue formazan product. In particular, 20ml of a 5mg/ml solution of MTT prepared in phosphate buffered saline was added to each well. After 4 hours incubation at 37^0, the medium was aspirated and replaced with 0.1ml dimethylsulphoxide. After vigorous shaking, the quantity of formazan

product formed was assessed by its optical density at 550nm. The absorbance is directly related to the number of surviving cells in the wells.

Cytotoxicity calculations were performed on the average of the two wells for each condition. The concentration of each MDR inhibitor giving a 50% reduction of the optical density relative to cells treated with doxorubicin alone was determined to give an EC_{50} value.

Results

In the above test the compounds of the specific Examples hereinabove had EC_{50} values in the range of 0.018 to 0.72mM. Thus, for example, the compound of Example 1 had an EC_{50} of 0.02mM, at least 100 times more potent than prototype MDR inhibitors including amiodarone (EC_{50} 3mM) and verapamil (3mM).

Administration of the compound of Example 1 to mice orally produced no visible toxic effects at single doses up to 300mg/kg.

The following are examples of pharmaceutical compositions according to the invention. The term 'Active Ingredient' as used hereinafter means a compound of the invention and may be for example the compound of Example 1.

Example A - Oral Tablet

	Per Tablet (mg)
Active Ingredient	50.0
Microcrystalline Cellulose	110.0
Lactose	67.5
Sodium Starch Glycolate	20.0
Magnesium Stearate	2.5
Total	250.0

The drug is sieved through a 250mm sieve and then the five powders are intimately mixed in a blender and compressed on 3/8 inch standard concave punches in a tabletting machine.

Example B - Oral Capsule

	Per Capsule (mg)
Active Ingredient	50.0
Microcrystalline Cellulose	66.5
Lactose USP	66.5
Sodium Starch Glycolate	15.0
Magnesium Stearate	2.0
Total	200.0

The drug is sieved through a 250mm sieve and then the five powders are intimately mixed in a blender and filled into No. 2 hard gelatin capsule shells on a capsule filling machine.

Example C - Injection for Intravenous Administration (10mg in 10mL)

	% w/w
Active Ingredient	0.1
Cancer chemotherapy agent	as required
Water for Injection to	100.0
Dilute hydrochloric acid to	pH 3.0

The active ingredient (and cancer chemotherapy agent where appropriate) is dissolved with mixing in the Water For Injection, adding acid slowly until the pH is 3.0. The solution is sparged with nitrogen and filtratively sterilized through a sterilized filter of 0.22 micron pore size. Under aseptic conditions this sterile solution is placed into sterile ampoules and the ampoules flame sealed.

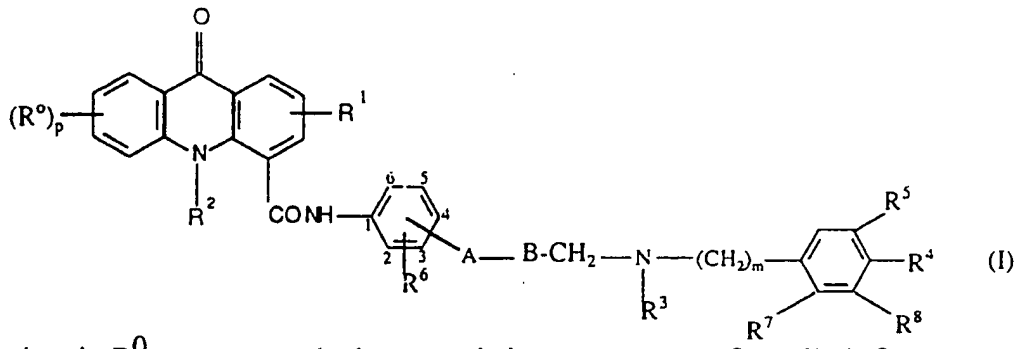
Example D - Oral Syrup

	% w/v
Active Ingredient	2.0
Cancer chemotherapy agent	as required
Dilute hydrochloric acid to	pH 3.0
Sobitol solution	60 v/v
Flavour	as required
Distilled water to	100

The active ingredient (and cancer chemotherapy agent where appropriate) is dissolved in some of the water with stirring by adding gradually the hydrochloric acid until the pH is 3.0. The sorbitol solution, flavour and the rest of the water are added and the pH re-adjusted to 3.0. The syrup is clarified by filtration through suitable filter pads.

CLAIMS :

1. A compound of formula (I)



(I)

wherein R^0 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino or nitro group;

p represents 1; or when R^0 represents C_{1-4}alkoxy may also represent 2 or 3;

R^1 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

A represents an oxygen or a sulphur atom, a bond or a group $(CH_2)_lNR^9$ (where l represents zero or 1 and R^9 represents a hydrogen atom or a methyl group);

B represents a C_{1-4} alkylene chain optionally substituted by a hydroxyl group, except that the hydroxyl group and moiety A cannot be attached to the same carbon atom when A represents an oxygen or sulphur atom or a group $(CH_2)_lNR^9$, or when A represents a bond B may also represent a C_{2-4}alkenylene chain;

R^3 represents a hydrogen atom or a C_{1-4}alkyl group;

m represents 1 or 2;

R^4 represents a hydrogen or a halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

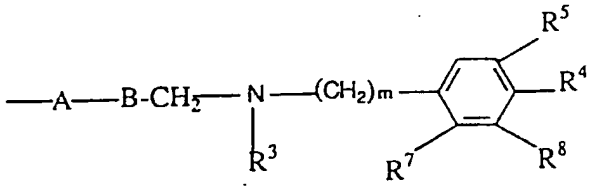
R^5 represents a hydrogen atom or a C_{1-4}alkoxy group;

R^6 represents a hydrogen atom or a C_{1-4}alkyl or C_{1-4}alkoxy group ;

R^7 represents a hydrogen atom or R^3 and R^7 together form a group $-(CH_2)_n-$ where n represents 1 or 2;

R^8 represents a hydrogen atom or a C_{1-4}alkoxy group;

the group



is attached at the benzene ring 3 or 4 position relate to the carboxamide substituent, provided that when the group is attached at the benzene ring 3 position then R^6 must be attached at the benzene ring 6 position;

and salts and solvates thereof.

2. A compound according to Claim 1 in which R^0 represents a hydrogen or fluorine atom, or a C_{1-4}alkoxy, C_{1-4}alkyl or C_{1-4}alkylthio group and R^1 represents a hydrogen atom.

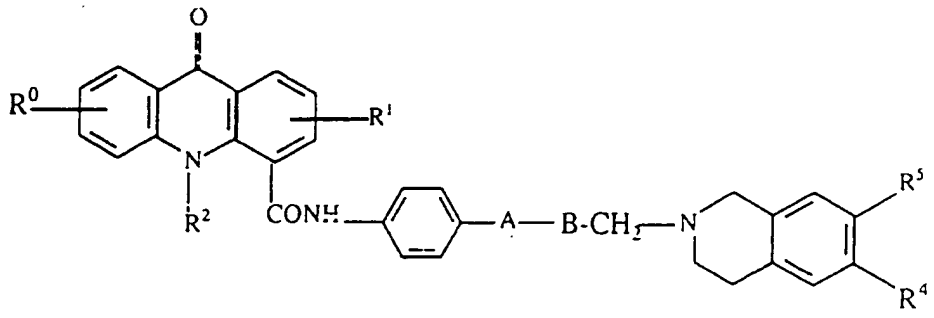
3. A compound according to Claim 1 or Claim 2 in which an R^0 group is situated at the 5-position of the acridone molecule.

4. A compound according to any preceding claim in which R^2 represents a hydrogen atom.

5. A compound according to any preceding claim in which R^4 and R^5 each represent a C_{1-4}alkoxy group and R^8 represents a hydrogen atom.

6. A compound according to any preceding claim in which m represents 1 and R^3 and R^7 together form a group $-(CH_2)_2-$.

7. A compound of formula (Ia)



(Ia)

wherein R^0 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy,C_{1-4}alkylthio or nitro group;

R^1 represents a hydrogen or halogen atom, or a C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio group;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

A represents an oxygen or a sulphur atom or a bond;

B represents an unsubstituted C_{1-4}alkylene chain;

R^4 and R^5 each independently represents a C_{1-4}alkoxy group; and physiologically acceptable salts and solvates thereof.

8. A compound according to Claim 7 in which R^0 represents a hydrogen or fluorine atom or a C_{1-4}alkoxy or C_{1-4}alkyl group, R^1 and R^2 each represent a hydrogen atom and R^4 and R^5 each represent a C_{1-4}alkoxy group.

9. A compound according to Claim 8 in which the R^0 group is situated at the 5-position of the acridone molecule.

10. A compound according to Claim 1 which is 9,10-dihydro-5-methoxy-9-oxo-N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-4-acridinecarboxamide and physiologically acceptable salts and solvates thereof.

11. A compound according to Claim 1 selected from :

9,10-dihydro-5-methoxy-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

5-fluoro-9,10-dihydro-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methoxy-9-oxo-N-[4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propoxy]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methyl-9-oxo-N-[4-[[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]thio]phenyl]-4-acridinecarboxamide;

9,10-dihydro-5-methoxy-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-9-oxo-4-acridinecarboxamide;

9,10-dihydro-N-[2-methoxy-4-[3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]phenyl]-5-methyl-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

12. A compound according to Claim 1 selected from :

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]- 9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[(3,4-dimethoxyphenyl)methyl]methylamino]butyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[5-[[(3,4-dimethoxyphenyl)methyl]methylamino]pentyl]phenyl]-5-fluoro-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethylamino] phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propyl]thio] phenyl]-9,10-dihydro-5-fluoro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methylthio-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methyl-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[4-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]butyl]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethyl]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]- 9,10-dihydro-2-(methylthio)-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propoxy]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethoxy]phenyl]- 9,10-dihydro-9-oxo-4-acridinecarboxamide;

N-[4-[3-[[(3,4-dimethoxyphenyl)methyl]methylamino]propoxy]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridinecarboxamide;

N-[4-[[2-[[(3,4-dimethoxyphenyl)methyl]methylamino]ethyl]thio] phenyl]-9,10-dihydro-9-oxo-4-acridinecarboxamide;

and physiologically acceptable salts and solvates thereof.

13. A compound according to any preceding claim for use in therapy.

14. A compound according to any preceding claim for use in the treatment of a mammal which is suffering from cancer, to improve or increase the efficacy of an antitumour drug, or increase or restore sensitivity of a tumour to an antitumour drug, or reverse or reduce resistance of a tumour to an antitumour drug.

15. Use of a compound according to any of Claims 1 to 12 for the manufacture of a medicament for the treatment of a mammal suffering from cancer, to improve or increase the efficacy of an antitumour drug, or increase or restore sensitivity of a tumour to an antitumour drug, or reverse or reduce resistance of a tumour to an antitumour drug.

16. A method of treatment of a mammal which is suffering from cancer, which method comprises administering to said mammal an effective amount of a compound according to any of Claims 1 to 12 to improve or increase the efficacy of

an antitumour drug, or increase or restore sensitivity of a tumour to an antitumour drug, or reverse or reduce resistance of a tumour to an antitumour drug.

17. A pharmaceutical composition which comprises a compound according to any of Claims 1 to 12 together with one or more physiologically acceptable carriers or excipients.

18. A pharmaceutical composition which comprises an active amount of a compound according to any of Claims 1 to 12 for use in the treatment of a mammal which is suffering from cancer, to improve or increase the efficacy of an antitumour drug, or increase or restore sensitivity of a tumour to an antitumour drug, or reverse or reduce resistance of a tumour to an antitumour drug.

19. A pharmaceutical composition according to Claim 17 or Claim 18 comprising a compound according to Claim 10.

20. A pharmaceutical composition according to any of Claims 17 to 19 in a form suitable for oral, buccal, parenteral or rectal administration.

21. A pharmaceutical composition according to any of Claims 17 to 20 in unit dosage form.

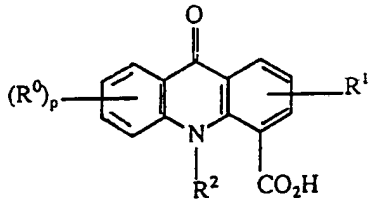
22. A product containing a compound according to any of Claims 1 to 12 and an antitumour drug as a combined preparation for simultaneous, separate or sequential use in treating cancer.

23. A compound according to any of Claims 1 to 12 and an antitumour drug in the presence of each other in the human or non-human animal body for use in treating cancer.

24. Product or process according to any of Claims 14 to 23 (except Claim 17) wherein the antitumour drug is selected from Vinca alkaloids, anthracyclines, taxol and derivatives thereof, podophyllotoxins, mitoxantrone, actinomycin, colchicine, gramicidine D, amsacrine or any drug having cross-resistance with the above drugs characterised by the so-called MDR phenotype.

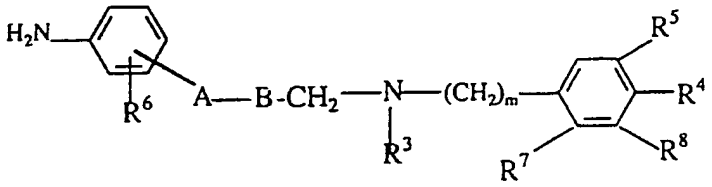
25. A process for the preparation of a compound according to Claim 1 which comprises :

(A) reacting a compound of formula (II)



(II)

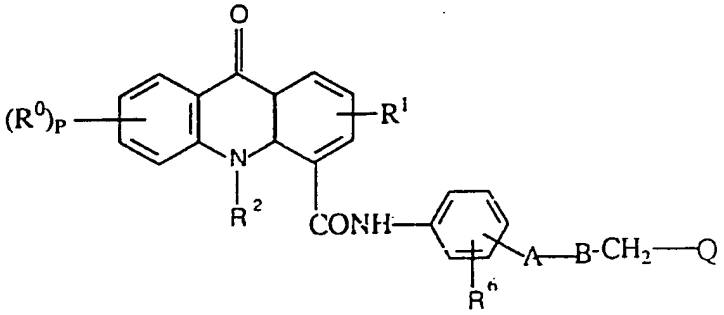
with a compound of formula (III)



(III)

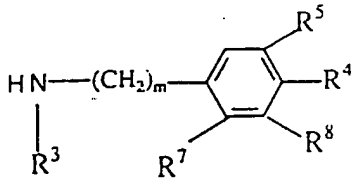
in the presence of a coupling reagent; or

(B) reacting a compound of formula (IV)



(IV)

(wherein Q represents a halogen atom) with a compound of formula (V)



(V)

or a salt thereof in the presence of an acid acceptor; with salt formation as an optional step subsequent to process (A) or (B).

26. Compounds according to any of Claims 1 to 12 substantially as herein described.

27. Compositions according to any of Claims 17 to 21 substantially as herein described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/00020

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 219/06 C 07 D 401/12 A 61 K 31/435
A 61 K 31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0098098 (DEVELOPMENT FINANCE CORP. OF NEW ZEALAND) 11 January 1984, see claims ---	1,13-23
A	Journal of Medicinal Chemistry, vol. 31, no. 3, March 1988, (Washington, US), B.D. PALMER et al.: "Potential antitumor agents. 54. Chromophore requirements for in vivo antitumor activity among the general class of linear tricyclic carboxamides", pages 707-712, see the whole document ---	1,13-23
A	Journal of Medicinal Chemistry, vol. 30, no. 4, April 1987, (Washington, US), W.A. DENNY et al.: "Potential antitumor agents. 49. 5-Substituted derivatives of N-[2-(Dimethylamino)ethyl]-9-aminoacridine-4-carboxamide with in vivo solid-tumor activity", pages 658-663, see the whole document -----	1,13-23

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05-03-1992	31. 03. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	[illegible] JORGENSEN

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SEC ND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

"Remark: Although claims 16,22,23 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compound or composition".

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200020 SA 54608

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/03/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0098098	11-01-84	JP-A- 59007171	14-01-84
		US-A- 4590277	20-05-86